EXHIBIT 146

ABSTRACT

Context: Use of nonsteroidal anti-inflammatory drugs (NSAIDs) is associated with upper gastrointestinal (GI) toxicity caused by inhibition of GI mucosal cyclooxygenase (COX)-1. Celecoxib specifically inhibits COX-2 and has demonstrated a low potential for producing GI injury.

Objective: To compare the incidence of significant upper GI toxicity in patients with rheumatoid arthritis (RA) or osteoarthritis (OA) treated with 2- to 4-times the maximum therapeutic doses of celecoxib, respectively, versus two NSAID comparators administered at standard therapeutic doses.

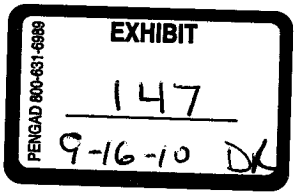
Design: Randomized, multicenter, double-blind trial from October 1998 through January 2000. All patients were provided the opportunity to complete at least six months of treatment.

Setting: Three hundred eighty clinical sites in the United States and Canada.

Patients: A total of 7,968 patients aged 18 years and older with OA (n= 5,746) or RA (n=2,183) who met inclusion criteria were randomized; 4,575 (57%) patients completed 6 months of treatment or withdrew prior to 6 months.

Interventions: Patients were randomized to receive celecoxib 400 mg twice daily (n=3,987), ibuprofen 800 mg three times daily (n=1,996) or diclofenac 75 mg twice daily (n=1,985) in 2:1:1 proportions. Concomitant low dose aspirin use (≤325 mg daily) for cardiovascular prophylaxis was permitted.

Main Outcome Measures: Incidence of upper GI ulcer complications (bleeding, perforation and obstruction) and symptomatic ulcers, or ulcer complications alone, for celecoxib versus NSAIDs that met pre-specified criteria judged by a blinded expert adjudication committee.



Results: For the entire cohort, the annualized incidence rates of upper GI ulcer complications alone, or combined with symptomatic ulcers, for celecoxib vs. NSAID comparators were 0.76% vs. 1.45% (p=0.092; relative risk = 0.53; 95% confidence interval (CI) 0.26 to 1.11) and 2.08% vs 3.54% (p=0.023; relative risk = 0.59; 95% CI 0.38 to 0.94). Removing the confounding effect of concomitant aspirin use, the annualized incidence rates of upper GI ulcer complications alone, or combined with symptomatic ulcers, for celecoxib vs. NSAID comparators were 0.44% vs.1.27% (p=0.037; relative risk = 0.35; 95% CI 0.14 to 0.98) and 1.40% vs 2.91% (p=0.017; relative risk = 0.48; 95% CI 0.28 to 0.89). Overall, celecoxib was better tolerated than NSAID comparators as fewer celecoxib-treated patients experienced GI, hepatic, renal or hemostasis-related adverse effects. No difference was noted in the incidence of thromboembolic cardiovascular events (myocardial infarction, cerebrovascular accidents) between celecoxib and NSAID comparators irrespective of aspirin use.

Conclusion: Celecoxib, at 2- to 4-times the maximally effective RA and OA doses, was associated with a lower incidence of significant upper GI toxicity and other adverse effects than NSAID comparators at standard therapeutic doses. This study validates celecoxib's unique mechanism of action and intrinsic general safety profile.

Key words: ulcer complications, symptomatic ulcers, cyclooxygenase, NSAIDs, celecoxib

Word Count: 3730 (*manuscript*), 431 (abstract)

INTRODUCTION

Musculoskeletal disorders are extremely common and represent a frequent cause of health care resource utilization.[1] For such disorders, nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used in a ~~mainstay of~~ clinical care and are ~~the~~ preferred ~~agent~~ by patients.[2-4] Well-established limitations of NSAID therapy include the risk of developing significant injury to the upper gastrointestinal (GI) tract, primarily ulceration or complications resulting from an ulcer such as perforation, gastric outlet obstruction and hemorrhage. Based on epidemiological and controlled trial experience, there is an estimated two- to ten-fold greater risk for upper GI injury in NSAID users when compared to nonusers.[5-11] The annualized incidence rate of upper GI ulcer complications and symptomatic ulcers in NSAID users ranges from 2 to 4% and 1 to 2% for ulcer complications alone.[12-16]

It is known that NSAIDs inhibit cyclooxygenase (COX), the enzyme responsible for the conversion of arachidonic acid to prostaglandins.[17] The ulcerogenic effects of these agents are attributed to interference with prostaglandin formation, thereby, leading to inadequate mucosal protection in the upper GI tract.[18;19] COX exists in two isoforms.[20-23] COX-1 is a ubiquitous constitutive isozyme; both gastrointestinal prostaglandins and platelet-derived thromboxane A_2 are formed exclusively from COX-1. Alternatively, COX-2 is largely a cytokine-induced isozyme producing prostaglandins that mediate pain and inflammation.[24-30] NSAIDs inhibit both COX-1 and COX-2 to varying degrees.[31;32] Thus, the therapeutic effects of NSAIDs are derived from inhibition of COX-2, while the adverse effects of these agents within the upper GI tract or with respect to platelet function arise from inhibition of COX-1 activity.

Celecoxib (Celebrex) is a recently approved agent for treating the inflammation and pain of OA and RA ~~arthritis~~ that specifically inhibits COX-2. Celecoxib appears to have little potential to produce upper GI injury as evidenced by a four-fold to six-fold lower association with gastroduodenal ulceration than either naproxen or diclofenac in endoscopic studies.[33;34] In these same trials, the risk of gastroduodenal ulceration in celecoxib-treated patients was comparable to placebo. A pooled analysis of 14 randomized controlled trials of arthritis patients also indicated that the incidence of upper GI ulcer complications associated with celecoxib was eight-fold lower than that found with diclofenac, ibuprofen and naproxen combined.[16]

In order to establish the distinct nature of the underlying biochemical mechanism of celecoxib more rigorously, however, it was essential to perform a prospective, randomized, double-blind study to determine the incidence of upper GI ulcer complications alone or combined with symptomatic gastroduodenal ulcers among arthritis patients chronically receiving celecoxib or NSAIDs. To clearly establish that celecoxib is COX-1 sparing, our study compared celecoxib administered at 2- to 4-times the maximum effective doses for RA and OA, respectively, to common therapeutic doses of ibuprofen and diclofenac, two non-specific NSAIDs commonly used to treat OA and RA. Concomitantly, this study served to assess more broadly the safety of celecoxib at supratherapeutic doses with respect to other potentially mechanism-based, as well as idiosyncratic, toxicities.

METHODS

Study Population

Men and women outpatients 18 years of age and older were eligible to participate in the study if they were diagnosed with OA or RA evident for 3 months or longer and were expected to require continuous treatment with an NSAID for the duration of the trial. Patients were excluded from the study participation if they had active GI, renal, hepatic, or coagulation disorders; malignancy (unless removed surgically with no recurrence within 5 years); esophageal or gastroduodenal ulceration within the previous 30 days; a history of gastric or duodenal surgery other than an oversew; or known hypersensitivity to COX-2 inhibitors, sulfonamides, ibuprofen, or diclofenac. Women were excluded if they were pregnant, might become pregnant, or were lactating.

Study Protocol

This prospective, randomized, double-blind trial was conducted at 380 centers in the United States and Canada from December 1998 to January 2000 in accordance with the principles of good clinical practice and the Declaration of Helsinki. The protocol was approved by the institutional review board at each study site and all patients were required to provide written informed consent.

Prior to enrollment, patients completed a physical examination and clinical laboratory testing, including a baseline serological test for *Helicobacter pylori* antibodies (FlexSure, Beckman-Coulter, Palo Alto, CA). After a baseline visit, follow-up clinic visits took place at weeks 4, 13, 26, and every 13 weeks thereafter (if necessary) after the initial dose of medication.

Monitoring for adverse events and clinical laboratory testing were repeated at all follow-up visits. All patients were given the opportunity to complete a minimum of 6 months of treatment.

Treatment

Patients were randomly assigned by a computer-generated randomization schedule to receive either celecoxib 400 mg BID or the comparator NSAID (ibuprofen 800 mg TID or diclofenac 75 mg BID) on a 2:1:1 basis. All treatment regimens were fully masked to ensure they were identical in appearance and that patients took the same number of capsules.

Concomitant Medications

NSAIDs (except for stable doses of aspirin up to 325 mg daily); anti-ulcer drugs (except for single dose antacid use daily or multiple dose use up to 7 days each month); antibiotics used alone or in combination with omeprazole, lansoprazole, and ranitidine for treatment of *H. pylori* infection; and antineoplastics were prohibited during the course of the study. Use of oral, intramuscular, and intra-articular glucocorticoids, and DMARDs were permitted.

Clinical Assessments

Investigators were instructed to identify and report all potential upper GI ulcer complications. Evaluation of such events was outlined in a pre-specified algorithm structured to reproduce clinical practice norms. Evaluation was required for any of the following presentations: severe acute abdominal pain or acute abdomen; intractable abdominal pain with nausea or vomiting; hematemesis or melena; acute hypovolemia or hypotension; history of melena within the past

14 days or black stool representing a change in normal pattern; development of postural dizziness or lightheadedness, or syncope; history of vaguely characterized dark stool, or dark stool within the past 14 days or with concurrent iron or bismuth ingestion; history of hematochezia, or anal or rectal bleeding after elimination; development of new anemia or decrease in hematocrit of 5% of more; development of dyspepsia, abdominal pain, or nausea or vomiting; or development of heme-positive stools. Endoscopy was encouraged to document bleeding lesions but could also be performed if indicated by the investigator's clinical judgement.

All documentation relating to potential ulcer complications was forwarded to a Gastrointestinal Events Committee (comprised of Jay Goldstein, MD, Naurang Agrawal, MD, Glenn Eisen, MD, and William Stenson, MD). The Committee was established to review and adjudicate all potential events according to prospectively established upper GI ulcer complication definitions as provided in Table 1. The Committee collectively reviewed each case in a blinded fashion and assigned it by consensus as either meeting or not meeting the definition of an upper GI ulcer complication. Symptomatic ulcers comprised those cases that did not meet the definition of an ulcer complication, but did have endoscopic or x-ray evidence of a gastric or duodenal ulcer as judged by the Committee. All patients with symptomatic ulcers or ulcer complications were withdrawn from the study.

Statistical Analysis

The sample size calculations were based on the assumption that the annualized incidence of upper GI ulcer complications would be 0.3% for celecoxib and 1.2% for NSAIDs. To detect

this difference with a 5% significance level (two-sided) and a power of 85% and assuming a 30% withdrawal rate, a sample size of 4,000 patients was required for the celecoxib group and 2,000 patients for each NSAID group.

Homogeneity of the treatment groups at baseline was analyzed by using the chi-square test for categorical variables and two-way ANOVA with treatment and center effects for continuous variables. All statistical analyses were conducted on the intent-to-treat populations that consisted of all patients who received at least one dose of assigned study medication. Time-to-event analyses of upper GI ulcer complications alone or combined with symptomatic ulcers were performed based on Kaplan-Meier estimates of cumulative event rates, but are expressed in the text as annualized incidence rates. Log-rank tests were used to compare the incidence rates based on the Kaplan-Meier estimate. The effect of potential risk factors for the development of an ulcer complication (including but not limited to concurrent aspirin use) were pre-specified and analyzed by Cox proportional hazards model. Treatment-related differences in the incidence of adverse effects or clinical laboratory changes were determined by Fisher's exact test.

need to state the mean length of therapy? 9 mos.?

RESULTS

A total of 7,968 patients were enrolled. Of these, 3,987 patients were treated with celecoxib 400 mg BID and 3,981 patients were treated with NSAIDs (1,996 received ibuprofen 800 mg TID and 1,985 received diclofenac 75 mg BID). Total patient-years of exposure were 1,473 and 1,377 in the celecoxib and NSAID treatment groups, respectively. There were no clinically meaningful differences in baseline characteristics between groups (Table 2). Mean age overall was 60 years (range 18-90 years); 38% of the patients were 65 years or older, 69% were women and 73% were diagnosed with OA. Approximately, 10% of the patients in each group had a prior medical history of a peptic ulcer or upper GI bleeding and over 20% of the patients were taking low dose aspirin (≤325 mg daily) for cardiovascular prophylaxis. Approximately 57% of the patients (n=4,573) completed six months of treatment. Figure 1 shows reasons for early discontinuation from the study. More patients in the NSAID treatment group withdrew from the study for either adverse effects or for lack of efficacy than did celecoxib-treated patients ($p<0.05$). No patients were lost to follow-up.

The crude rate of potential upper GI ulcer complications reported by investigators to the Events Committee over 6 months was significantly lower in celecoxib-treated patients than with NSAIDs (16.0% vs 12.6%, $p<0.001$). All reports were reviewed by the Events Committee and a total of 261 cases of potential upper GI ulcer complications were selected for adjudication (the remainder being cases of either isolated GI symptoms or anemia without further evidence of a potential event). Upon adjudication, the Events Committee identified 35 upper GI ulcer complications and another 48 cases that represented symptomatic, but

12.6% 16.0%

uncomplicated, gastroduodenal ulcers (Table 3). All but one of the upper GI ulcer complications (a gastric outlet obstruction in a celecoxib-treated patient) represented bleeding events in which an ulcer or large erosion was associated with either visual evidence of bleeding, melena, or occult blood-positive stools and a decrease in hematocrit or hemoglobin. Four upper GI ulcer complications (2 in celecoxib patients and 2 in NSAID-treated patients) were censored from the analysis owing to the timing of the event as prespecified by the Events Committee (within 48 hours after the first dose day or after 14 days after the last known dose). The remaining 178 cases were judged by the Committee to represent neither an upper GI ulcer complication nor a symptomatic ulcer and were assigned a diagnosis under the categories listed in Table 3.

The annualized incidence of upper GI ulcer complications in celecoxib-treated patients based on 6 months exposure was approximately one-half the rate observed in patients taking NSAIDs (0.76% vs 1.45%, p=0.092, Figure 2 top panel). The relative risk over 6 months for celecoxib compared to NSAIDs was 0.53 (95% CI, 0.26-1.11). The annualized incidence of upper GI ulcer complications plus symptomatic ulcers with celecoxib was significantly lower than with NSAIDs (2.08% vs 3.54%, p=0.023, Figure 2 top panel). The relative risk over 6 months for celecoxib compared to NSAIDs was 0.59 (95% CI, 0.38-0.94).

Based on survival analyses with a Cox proportional hazard model, low dose aspirin use was found to have a statistically significant effect (p=0.005) on the incidence of upper GI ulcer complications (alone or in combination with symptomatic ulcers) in the celecoxib-treated patients. Within the celecoxib treatment group, an upper GI ulcer complication was nearly 4-

fold more common in aspirin users occurring in 6 of 833 patients (0.7%) taking low dose aspirin vs 5 such events in 3,154 (0.2%) non-aspirin users. Low dose aspirin use did not have a significant effect on the rate of upper GI ulcer complications in patients receiving NSAIDs (p=0.21). In consequence, the non-aspirin using cohort was examined independently.

The annualized incidence of upper GI ulcer complications over 6 months in non-aspirin users was significantly lower with celecoxib vs NSAIDs (0.44% vs 1.27%, p=0.037, Figure 2 bottom panel). The relative risk over 6 months for celecoxib compared to NSAIDs was 0.35 (95% CI, 0.14-0.98). The annualized incidence of upper GI ulcer complications plus symptomatic ulcers over 6 months in patients not taking aspirin users was also significantly lower with celecoxib than with NSAIDs (1.40% vs 2.91%, p=0.017, Figure 2 bottom panel). The relative risk over 6 months for celecoxib compared to NSAIDs was 0.48 (95% CI, 0.28-0.89).

Celecoxib, administered at 2- to 4-times the maximum effective RA and OA doses respectively, was safe and generally well-tolerated when chronically administered as compared to standard therapeutic doses of either ibuprofen or diclofenac. The adverse effects with the highest incidence in either treatment group were dyspepsia, upper respiratory infection, headache, abdominal pain and diarrhea.

Celecoxib was associated with better GI tolerability than NSAID treatment. The overall incidence of GI adverse effects experienced by patients taking celecoxib was significantly lower than with NSAIDs (40% vs 45%; p<0.001) as was the rate of withdrawal due to GI

intolerability (Table 4). Of the most commonly reported GI adverse effects, dyspepsia, abdominal pain, nausea, and constipation were significantly less common ($p<0.001$) with celecoxib than with NSAIDs (Table 4). Similar effects were seen in the cohort of patients not taking low dose aspirin.

Significantly less hemostasis-related adverse effects (anemia, ecchymoses, hematochezia) and withdrawals due to such were observed in patients receiving celecoxib when compared to NSAID-treated patients (Table 4). Celecoxib was also associated with a lower incidence ($p<0.05$) of clinically meaningful reductions in hematocrit or hemoglobin for the entire patient cohort (Figure 3). This difference persisted when all patients with potential upper GI events were excluded from the analysis, thus removing all patients with ulcer complications, symptomatic ulcers or other diagnosed GI pathology (Figure 3). In parallel with changes seen in hematocrit and hemoglobin, serum iron to iron binding capacity ratios tended to increase on celecoxib and decrease on NSAIDs (+1.4% vs -2.4%, $p<0.05$).

, Table 4

As shown in Figure 4, the incidence of serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevations that exceeded 3 times the upper limit of normal was 5- to 10-fold higher ($p<0.05$) in patients receiving NSAIDs than with celecoxib. ~~Similarly, investigators reported a significantly higher ($p<0.05$) incidence of elevated serum transaminases with NSAID treatment (Table 4)~~. Study withdrawals due to elevated serum transaminases were also higher in patients receiving NSAIDs. Most liver function enzyme elevations occurred in patients receiving diclofenac.

The incidence rates of renal-related adverse effects such as peripheral edema, hypertension (or aggravated hypertension) were similar between the treatment groups (Table 4). However, an elevated serum creatinine was noted more frequently by investigators in patients on NSAIDs than in patients on celecoxib ($p<0.05$). Also, a greater number of patients ($p<0.05$) receiving NSAIDs were found with elevations in serum creatinine levels above 2 mg/dL and/or BUN values above 40 mg /dL than with celecoxib (Figure 4). Celecoxib was associated with a significantly higher incidence ($p<0.05$) of rash and pruritus and study withdrawals due to cutaneous adverse effects as compared to NSAID therapy (Table 4). The incidences of thromboembolic cardiovascular events were similar in the two treatment groups (Table 4). No treatment differences in such events were apparent in the patients in the two treatment groups not taking aspirin for cardiovascular prophylaxis (Table 4).

Serious adverse effects (representing hospitalizations or malignancies detected during study participation) were reported for 4.3% of patients receiving celecoxib and 4.2% of NSAID patients. The most common serious adverse effects were accidental fractures, pneumonia, cardiac failure, myocardial infarction and coronary artery disorders consistent with expected co-morbidities in this patient population. No serious rashes or unexpected serious adverse events were observed in patients on celecoxib. No treatment-related differences were observed.

DISCUSSION

Our study establishes that celecoxib when used chronically at 2- to 4-times the maximum effective doses for RA and OA, respectively, is associated with a lower incidence of upper GI ulcer complications and symptomatic ulcers than comparator NSAIDs (ibuprofen and diclofenac) at standard therapeutic doses. This study thus directly ~~addresses the critical safety issue inherent to COX-2 specificity, namely that~~ COX-2 specific inhibitors are associated with a reduction in upper GI toxicity relative to non-specific COX inhibitors. In addition, the data presented herein support the overall safety and tolerability of celecoxib, part of which may be mechanism-dependent and part of which may be ~~specific to the~~ pharmacology of this ~~agent. It is worth noting that a~~ clinical trial using an NSAID at supratherapeutic doses (similar to those used for celecoxib in the current trial) would not be feasible given the known toxicology of NSAIDs.[35-38]

The ~~driving force behind the~~ development of COX-2 specific inhibitors has been a widening appreciation of the mechanism-based GI toxicity of NSAIDs. The public health impact of NSAID-related upper GI toxicity is substantial. Based on the NSAID-attributable incidence of ulcer complications, it has been estimated that such complications lead to approximately 107,000 hospitalizations and 16,500 deaths yearly in the US.[11]

In this study, the incidence of an upper GI ulcer complication combined with symptomatic ulcers associated with NSAID comparators was 3.54%, with an incidence of ulcer complication alone of 1.45%. In comparison, the corresponding rates associated with supratherapeutic doses of celecoxib in this study were 2.08% and 0.76%, respectively, the

difference in symptomatic ulcers and ulcer complications being statistically significant. The lack of a statistical significant separation of upper GI complications associated with celecoxib when compared to NSAIDs in the entire study cohort was largely ~~a function of~~ due to the higher than expected event rate observed in the celecoxib treatment group relative to the previously reported annualized incidence rate of 0.2% obtained from a pooled analyses of 14 randomized controlled trials ranging from 2 to 24 weeks in duration.[16]

event rate

This increase was attributable to concurrent low-dose aspirin use. The percentage of patients using low-dose aspirin for cardiovascular prophylaxis was nearly double that seen in other endoscopic trials that we have conducted recently, albeit within the range reported for the general population.[39] Low-dose aspirin therapy also has been associated with serious GI complications in numerous epidemiological studies.[40-43] In our study, aspirin increased the relative risk of an upper GI ulcer complication by nearly four-fold in patients on celecoxib, but not with the actual NSAID comparators.

Given the confounding effect of aspirin use, analysis of the non-aspirin users in this study addresses more directly the relative upper GI safety attributes of celecoxib vs comparator NSAIDs. In this analysis, celecoxib was associated with a significantly lower incidence of upper GI ulcer complications and symptomatic ulcers vs. NSAIDs (1.40% vs 2.91%, respectively) as well as a significantly lower incidence of ulcer complications alone (0.44% vs 1.27%, respectively). The rate of ulcer complications in non-aspirin users on celecoxib (0.44%) is sufficiently close to the background rate in the population (0.1-0.4%) that the attributable risk of ulcer complications cannot be estimated with accuracy.[9;10;12;13;44-47]

In addition to the assessment of GI safety, the present study provides data to characterize the overall safety profile of celecoxib. In particular, supratherapeutic doses of celecoxib were not found to have a side effect profile that differed remarkably from the profile reported elsewhere for doses two- to four-fold lower and representing the maximum therapeutic doses for RA and OA, respectively.[33;34;48] Moreover, the incidence rates for most common and uncommon adverse effects that occurred with celecoxib were below or similar to those seen with NSAID treatment with the exception of rash and pruritus.

An important finding of the present study is that celecoxib-treated patients had a significantly lower incidence of clinically significant decreases in hemoglobin or hematocrit when compared to NSAID-treated patients, even when patients with upper GI ulcer complications, symptomatic ulcers and other cases of potential upper GI events were excluded. Such decreases with NSAIDs were also associated with evidence of decreasing iron stores. These data together suggest chronic lower GI blood loss. NSAID-associated chronic blood loss from the lower GI tract may result from two non-mutually exclusive sources: (1) pre-existing lesions (e.g. polyps) that bleed due to the anti-platelet effects of these drugs, or (2) NSAID-associated enteropathy.[49;50] Thus, the diminution of significant GI blood loss observed with celecoxib may be due to the absence of platelet effects, reduced lower GI toxicity, or both. The potential clinical implication of the decreased incidence of chronic GI blood loss with celecoxib is a reduction in the incidence of anemia, which can add to the debility of chronic arthritis or possibly exacerbate co-morbidities (e.g. cardiovascular disease).

Supratherapeutic doses of celecoxib were also better tolerated than NSAIDs as evidenced by the decreased incidence of GI symptoms. Improved tolerability is important clinically as reflected by the significant difference in withdrawal rates for GI symptoms. Whether or not GI symptoms are COX-1 mediated, however, is uncertain. Although ulcer complications are often asymptomatic, NSAID intolerance has been identified as a risk factor for such complications.[11;51]

The clinical consequences of NSAIDs on the kidney are heterogenous and at present the relative importance of COX-1 and COX-2 in the human kidney is not well defined.[52] Regardless, celecoxib at supratherapeutic doses appeared to be associated with significantly less renal toxicity when compared to NSAID therapy. A treatment difference was evident for increases in serum creatinine suggesting a differential effect on glomerular filtration. This observation is consistent with a recently reported renal pharmacological study in elderly subjects.[53]

Although it has been hypothesized that COX-2 specific inhibitors might increase the risk of cardiovascular thromboembolic events via inhibition of vascular prostacyclin synthesis without a corresponding inhibition of platelet thromboxane, no such increase was evident in the current study.[54] In both the entire study population as well as the cohort not taking aspirin (who would conjecturally be most at risk of such an effect), the incidence of thromboembolic events were comparable between celecoxib and NSAIDs.

In conclusion, our results establish that celecoxib at doses 2- to 4-fold greater than the maximum therapeutic doses for RA and OA is associated with reduced upper GI toxicity when compared to standard therapeutic doses of NSAIDs. This finding confirms the COX-2 hypothesis, that is, that COX-2 specific agents will exhibit ~~diminished~~ decreased GI toxicity at ~~supra~~ therapeutic doses for OA and RA.[55] This improvement in GI safety was not tempered by other toxicities which emerged at supratherapeutic doses ~~establishing the intrinsic safety profile of celecoxib specifically~~. Our findings thus have significant healthcare implications with respect to optimal drug therapy for the treatment of OA, RA and other musculoskeletal disorders.

Two issues:

From cardiovascular risk: one enzyme patients studied to definitively prove the celecoxib does not have an ↑ risk?

In that all pts on NSA would be at high risk, the use of celecoxib in the not at high risk pt group supplying CV safety is not entirely known → do you have data on the non-NSA user and risk pts and in that group → did they have an increased risk??

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FIGURE LEGENDS

Figure 1: Flow chart of patient disposition

Figure 2: The annualized incidence (percentage of patients) of upper GI ulcer complications alone or combined with symptomatic gastroduodenal ulcers for the entire study population (top panel) and for the cohort of patients not taking low dose aspirin.

Figure 3: The percentage of patients with a decrease in hematocrit (Hct) of 10 percentage points or more from pretreatment, a decrease in hemoglobin (Hgb) of 2 gm/dL or more from pretreatment, or both. Results for the entire study population are shown on the left. On the right, the results for all patients excluding those with an upper GI ulcer complication, symptomatic ulcer or other diagnosed GI pathology are shown.

Figure 4: The percentage of patients with an increase in serum creatinine to a value of 2 mg/dL or more, an increase in blood urea nitrogen (BUN) to a value of 40 mg/dL, or both (top panel) and the percentage of patients with elevations in alanine aminotransferase (ALT) and asparate aminotransferase (AST) to a value three times the upper limit of normal (bottom panel).

Table 1. Definitions and Adjudication Criteria for Ulcer Complications

Event	Criteria for Confirmed Event
Gastric or duodenal perforation	A perforated lesion that required surgery. It could involve a laparoscopic repair, but only if evidence of the perforation was unequivocal, such as free air in the abdomen visible by x-ray, or peritoneal signs upon physical examination.
Gastric outlet obstruction	Gastric outlet obstruction was required to be diagnosed by the investigator, and the diagnosis was required to be supported by endoscopy (e.g., ulcer with a tight edematous pyloric channel) or by x-ray results (e.g., a dilated stomach, delayed barium emptying with clinical evidence of outlet obstruction and with an ulcer in the channel, or severe outlet narrowing and edema)

Upper GI bleeding	• hematemesis with a lesion (ulcer or large erosion) at endoscopy or x-ray
	• lesion (ulcer or large erosion) at endoscopy with evidence of active bleeding or stigmata of a recent hemorrhage (visible vessel or clot attached to the base of an ulcer)
	• melena with a lesion (ulcer or large erosion) at endoscopy or x-ray with evidence of serious bleeding, which included at least one of the following:
	  • decrease in hematocrit (of at least 5 percentage points) or decrease in hemoglobin (greater than 1.5 g/dL relative to baseline)
	  • signs of postural vital sign changes (increase in pulse rate of at least 20 bpm and/or decrease in systolic blood pressure of at least 20 mm Hg and/or in diastolic blood pressure of at least 10 mm Hg)
	  • transfusion of more than two units of blood
	  • blood in the stomach at endoscopy or nasogastric aspiration

Table 2. Baseline Characteristics and Patient Demographics

Characteristic	Celecoxib 400 mg BID (n = 3987)	NSAIDs (n = 3,981)
Mean age (range), y	60.6 (20-89)	59.8 (18-90)
>65 years of age (%)	39.1	37.3
>75 years of age (%)	12.2	11.3
Women, (%)	68.5	69.1
Race, (%)		
White	88.5	87.8
Black	7.5	8.1
Hispanic	2.7	2.8
Asian	0.8	0.7
Other	0.5	0.6
Primary disease, (%)		
RA	27.3	27.5
Mean (SD) duration of disease, y		
OA	10.2 (9.7)	10.1 (9.9)
RA	11.3 (9.9)	10.7 (9.6)
Potential Risk Factor (%)		
History of GI bleeding	1.7	1.5
History of GI ulcer	8.4	8.1
Positive *Helicobacter pylori* infection (%)	37.1	36.7
Tobacco use, (%)	15.8	14.9
Alcohol use, (%)	30.9	30.1
Concurrent medications, (%)		
Aspirin (≤325 mg daily)	20.9	20.4
Corticosteroids	30.2	29.3
Anticoagulants	0.5	0.9

Table 3. Number of Potential Cases Reported, Adjudicated Cases, Gastroduodenal Ulcers, and Ulcer Complications that Met Pre-specified Definitions

Category	Celecoxib 400 mg BID (n = 3,987)	NSAIDs (n = 3,981)
Total cases adjudicated	114	147*
Total cases not meeting the definition of a gastroduodenal ulcer or ulcer complication	82	96
Esophageal disease	16	14
Gastroduodenitis	16	19
Colonic or small bowel disease	2	6
Non-ulcer bleeding	18	21
Miscellaneous GI symptoms	24	24
Anemia	5	12
Cholelithiasis	1	-
Ulcer complications and gastroduodenal ulcers	32	51
Gastroduodenal ulcers	19	29
Ulcer complications†	13	22
Upper GI bleeding	10	20
Perforation	0	0
Gastric outlet obstruction	1	0

*p<0.001 vs celecoxib

†4 ulcer complications (2 in celecoxib patients and 2 in NSAID patients were censored from the analysis due to the timing of the event)

Table 4. Adverse Events

Characteristic	All Patients		Non-aspirin Cohort	
	Celecoxib 400 mg BID (n = 3995)	NSAIDs (n = 3987)	Celecoxib 400 mg BID (n = 3154)	NSAIDs (n = 3169)
Gastrointestinal				
Dyspepsia	14.4	18.0*	13.5	15.7*
Abdominal pain	9.7	13.1*	9.1	12.5*
Diarrhea	9.4	9.8	9.1	9.2
Nausea	6.9	9.3*	6.8	8.7*
Constipation	1.7	5.9*	1.5	5.4*
Withdrawals	10.8	13.8*	10.2	13.0*
Hepatic				
Elevated serum ALT or AST	0.9	3.2*	0.9	3.0*
Withdrawals	0.1	1.5*	0.1	1.4*
Bleeding-Related				
Anemia	2.2	4.4*	1.9	3.9*
Ecchymosis	0.7	0.8	0.7	0.8
Hematochezia	0.4	1.0*	0.3	0.9*
Withdrawals	0.3	0.6*	0.4	0.6
Renal				
Peripheral edema	2.8	3.5	2.9	3.4
Hypertension	1.7	2.3	1.5	2.0
Increased creatinine	0.7	1.2*	0.6	1.0
Withdrawals	1.2	1.0	1.2	1.0
Cardiovascular				
Cerebrovascular	0.1	0.3	<0.1	0.2
Myocardial infarction	0.3	0.3	<0.1	0.1
Angina	0.6	0.6	0.3	0.3
Withdrawals	0.3	0.4	0.3	0.2
Cutaneous				
Rash	5.5	2.6*	5.7	2.9*
Pruritus	2.3	1.5*	2.3	1.4*
Urticaria	0.6	0.4	0.3	0.1
Withdrawals	3.1	1.3*	3.4	1.5*

Figure 1

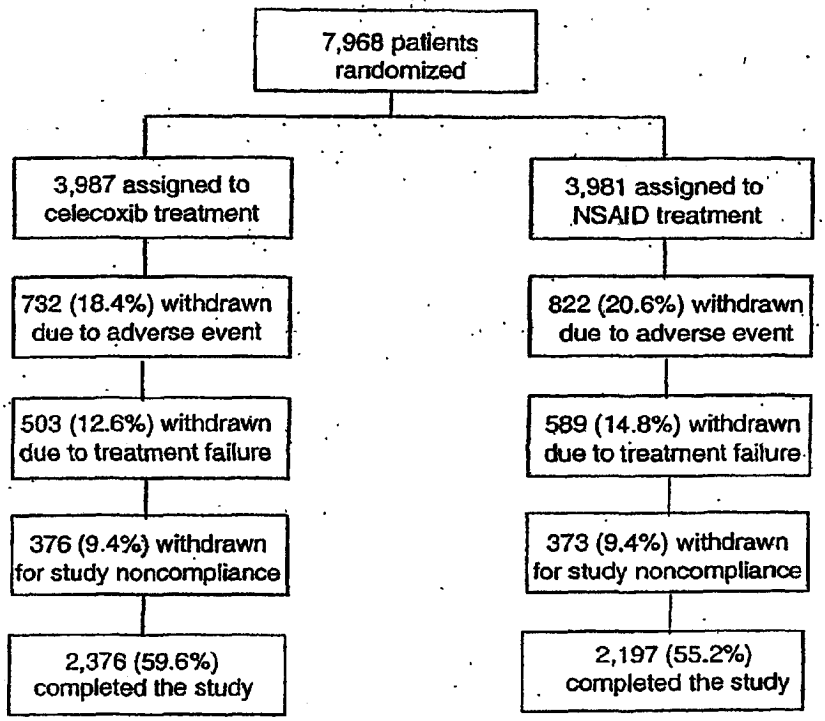
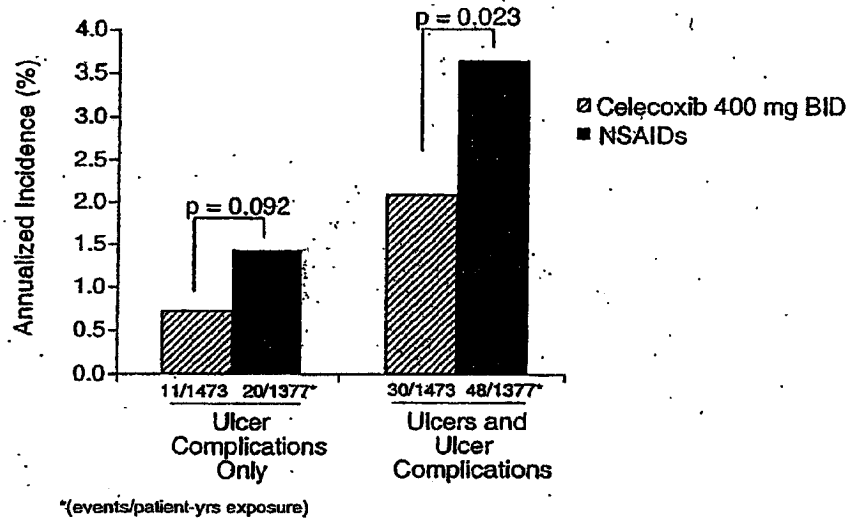

7,968 patients randomized
3,987 assigned to celecoxib treatment
3,981 assigned to NSAID treatment
732 (18.4%) withdrawn due to adverse event
822 (20.6%) withdrawn due to adverse event
503 (12.6%) withdrawn due to treatment failure
589 (14.8%) withdrawn due to treatment failure
376 (9.4%) withdrawn for study noncompliance
373 (9.4%) withdrawn for study noncompliance
2,376 (59.6%) completed the study
2,197 (55.2%) completed the study

Figure 2


Annualized Incidence (%)
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
p = 0.092
p = 0.023
11/1473 20/1377*
30/1473 48/1377*
Ulcer Complications Only
Ulcers and Ulcer Complications
Celecoxib 400 mg BID
NSAIDs
*(events/patient-yrs exposure)

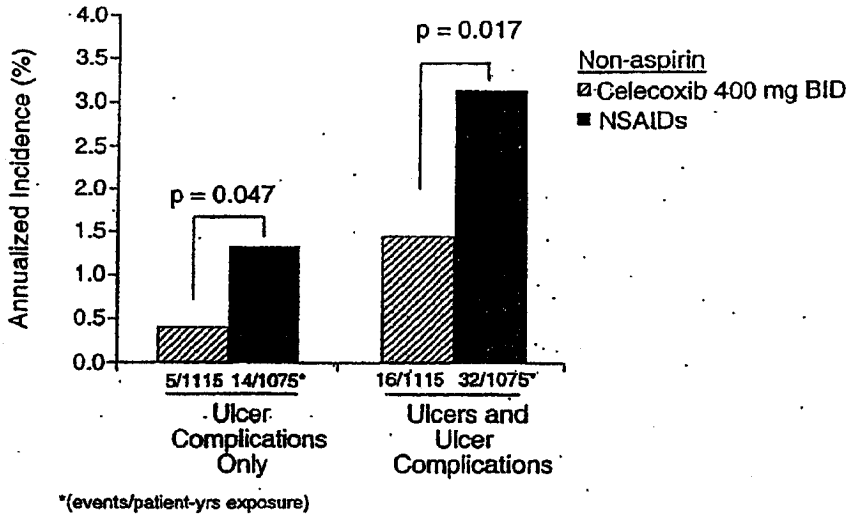

Annualized Incidence (%)
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
p = 0.047
p = 0.017
5/1115 14/1075*
16/1115 32/1075*
Ulcer Complications Only
Ulcers and Ulcer Complications
Non-aspirin
Celecoxib 400 mg BID
NSAIDs
*(events/patient-yrs exposure)

Figure 3

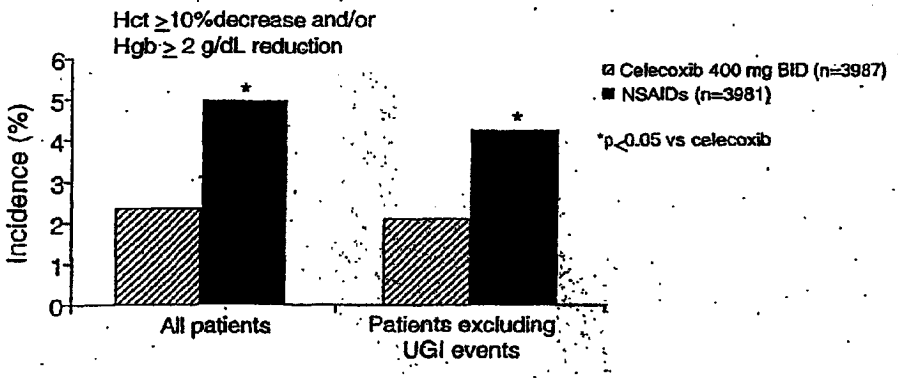

Hct ≥10%decrease and/or
Hgb ≥ 2 g/dL reduction
Incidence (%)
0
1
2
3
4
5
6
*
*
All patients
Patients excluding UGI events
Celecoxib 400 mg BID (n=3987)
NSAIDs (n=3981)
*p<0.05 vs celecoxib

Figure 4

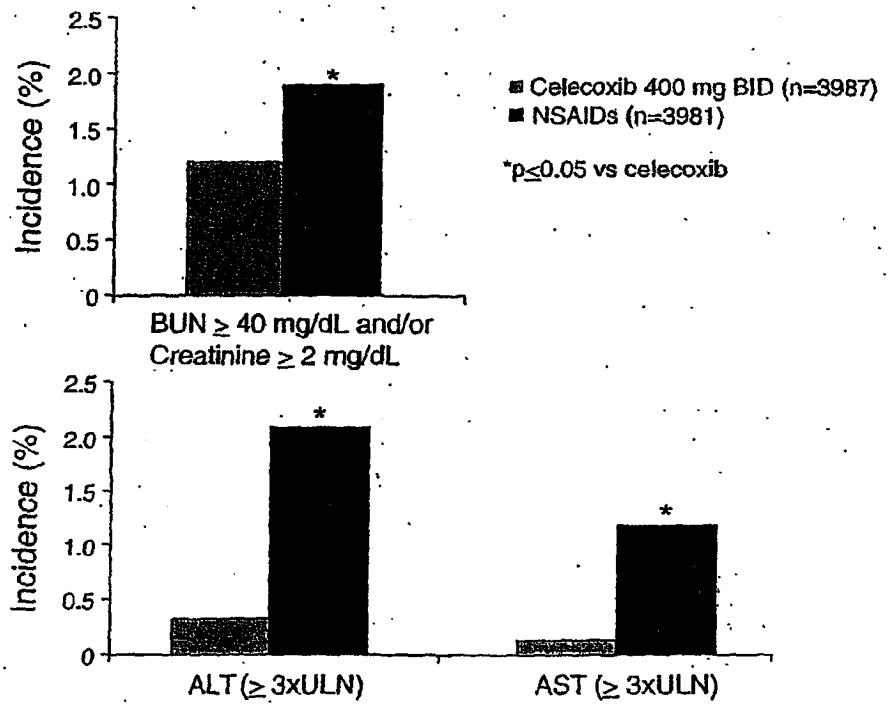

Incidence (%)
2.5
2.0
1.5
1.0
0.5
0
*
BUN ≥ 40 mg/dL and/or
Creatinine ≥ 2 mg/dL
Celecoxib 400 mg BID (n=3987)
NSAIDs (n=3981)
*p≤0.05 vs celecoxib
Incidence (%)
2.5
2.0
1.5
1.0
0.5
0
*
*
ALT (≥ 3xULN)
AST (≥ 3xULN)

EXHIBIT 147

From: ZHAO, WILLIAM W [PHR/1825]
Sent: Monday, June 19, 2000 4:17 PM
To: LEFKOWITH, JAMES B. [PHR/1825]; VERBURG, KENNETH M [PHR/1825]
Subject: CBX-0372814_RE: comments on added sentence to CLASS ms.

Jim,

Please see my change in blue.

William

-----Original Message-----
From: LEFKOWITH, JAMES B. [PHR/1825]
Sent: Monday, June 19, 2000 10:18 AM
To: ZHAO, WILLIAM W [PHR/1825]; VERBURG, KENNETH M [PHR/1825]
Subject: comments on added sentence to CLASS ms.

Statistical Analysis

Homogeneity of the treatment groups at baseline was analyzed by using the chi-square test for categorical variables and two-way ANOVA with treatment and center effects for continuous variables. Statistical analyses were conducted on the intent-to-treat population that consisted of all patients who received at least one dose of assigned study medication and on the population of patients not taking ASA (since ASA use was a predefined risk factor for GI events). ~~*Data were censored at 6 months because of the much higher than expected withdrawal rate (ca. 45% observed vs. ca. 25% expected) as well as evidence of progressive differential withdrawal of patients with NSAID GI risk factors and intolerance both within and between treatment groups which confounded standard analysis (because of depletion of susceptible patients and informative censoring, manuscript in preparation).ß*~~ Continue as one paragraph. Time-to-event analyses of upper GI ulcer complications alone or combined with symptomatic ulcers were performed based on Kaplan-Meier estimates of cumulative event rates over 6 months which was required minimum treatment duration. But in the text the annualized incidence rates (number of events per 100 patient-years of exposure or %) were expressed for summary. Log-rank tests were used to compare the time-to-event curves between treatments. The effects of potential risk factors for the development of a symptomatic ulcer and/or ulcer complication (including but not limited to concurrent ASA use) were analyzed by Cox proportional hazards model. The

EXHIBIT 440 4/11/11 LR

incidences of treatment-emergent adverse effects or clinical laboratory changes in the different treatment groups over 6 months were determined by Fisher's exact test. All p values and 95% confidence intervals are of the two-sided type.

EXHIBIT 148

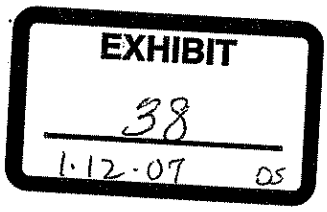
From: TAM, NANCY W [PHR/1825]
Sent: Tuesday, April 04, 2000 4:03 PM
To: VERBURG, KENNETH M [PHR/1825]
Subject: CBX-0367790_manuscript

Ken,

Below is the most recent version of the CLASS manuscript.

Nancy

CBX-0367791_CLAS
S_manuscript.v...



THE CELECOXIB LONG-TERM ARTHRITIS SAFETY STUDY (CLASS): REDUCED RISK FOR UPPER GASTROINTESTINAL BLEEDING, PERFORATION, AND OBSTRUCTION COMPARED TO DICLOFENAC AND IBUPROFEN

Running Title: Effects of Celecoxib on Ulcer Complications

Byline: Celecoxib Long-Term Arthritis Safety Study Group

Word Count: 4072/3000

ABSTRACT

Background: Use of nonsteroidal anti-inflammatory drugs (NSAIDs) has been strongly linked with upper gastrointestinal (GI) toxicity, and appears to result from inhibition of cyclooxygenase (COX)-1 and loss of prostaglandin-dependent mucosal protection. Celecoxib is a COX-2-specific inhibitor that has been shown to be as effective as naproxen and diclofenac in treating the inflammation and pain of osteoarthritis (OA) and rheumatoid arthritis (RA), with a lower risk of gastroduodenal ulceration. Based on these findings, we postulated that celecoxib would also be associated with a lower risk of upper GI ulcer complications. To test this theory, we compared the incidence rate of upper GI ulcer complications associated with celecoxib to that of diclofenac and ibuprofen in two companion, long-term, randomized, double-blind clinical trials.

Methods: Patients with OA or RA were enrolled into one of two studies simultaneously conducted for a period up to 65 weeks. In one study, patients were randomly assigned to receive celecoxib 400 mg BID (n = XX; XX patient-years) or ibuprofen 800 mg TID (n = XX; XX patient-years), while in the second study, patients were randomly allocated to treatment with celecoxib 400 mg BID (n = XX; XX patient-years) or diclofenac 75 mg BID (n = XX; XX patient-years). The primary outcome measure was the incidence of a clinically significant upper GI ulcer complication, prospectively defined as upper GI bleeding, perforation, or gastric outlet obstruction. All potential ulcer complications were reviewed and adjudicated by members of an expert committee, who were blinded to patients' treatments. By prospective design, the results of the two studies were analyzed in an integrated manner, combining the celecoxib groups into one group.

Results: The incidence of upper GI ulcer complications was lower for celecoxib-treated patients (XX%, XX of XX patients) than for patients receiving ibuprofen or diclofenac (XX%, XX of XX patients and XX%, XX of XX patients, respectively). The annualized incidences of upper GI ulcer complications for celecoxib, ibuprofen, and diclofenac were XX%, XX%, and XX%, respectively (p = XX for ibuprofen and XX for diclofenac). The frequency of GI-related adverse events was also lower in the celecoxib group (XX%, XX patients) than in the ibuprofen (XX%, XX patients) or diclofenac group (XX%, XX patients). Overall, celecoxib was better tolerated than NSAIDs as fewer celecoxib-treated patients (XX%, XX patients) withdrew from the studies than patients receiving ibuprofen (XX%, XX patients) or diclofenac (XX%, XX patients) due to any adverse effect.

Conclusion: At twice the highest therapeutic dose, long-term use of celecoxib is associated with a significantly lower frequency of upper GI ulcer complications than long-term use of therapeutic doses of ibuprofen or diclofenac. These results demonstrate that celecoxib has a much better overall GI safety profile than either ibuprofen or diclofenac when used chronically for the treatment of OA or RA.

Key words: Ulcer complication, bleeding, perforation, obstruction, NSAID, COX-2-specific inhibitor

Word count: 460/250

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used as treatments for osteoarthritis (OA) and rheumatoid arthritis (RA). It has been estimated that 13 to 15 million patients with arthritis in the U.S. require regular and often chronic treatment with NSAIDs.[1,2] Many studies have now documented an increased risk for the development of gastroduodenal ulceration or ulcer complication, such as upper gastrointestinal (GI) bleeding, perforation, or gastric outlet obstruction in patients taking NSAIDs. Based on epidemiological and controlled trial experience, there is an estimated five-fold greater risk for an ulcer complication in NSAID users and an annual incidence rate ranging from 1% to 2%.[3,4]

The ulcerogenic effects of NSAIDs are largely attributable to the effects of these agents on the production of gastrointestinal prostaglandins, which confer mucosal protection in the upper GI tract. NSAID-mediated regulation of prostaglandin synthesis involves inhibition of cyclooxygenase (COX), an enzyme that mediates the conversion of arachidonic acid to prostaglandins.[5,6,7] COX exists as two isoforms: COX-1 and COX-2.[8,9,10,11] COX-1 is a constitutively expressed isoform, while COX-2 is an inducible isoform that is rapidly and highly induced at sites of inflammation. Thus, the therapeutic effects of NSAIDs are derived from their ability to inhibit COX-2 activity, while the adverse effects of these agents within the upper GI tract arise from inhibition of COX-1 function.

Celecoxib (Celebrex™) is a recently approved agent for treating the inflammation and pain of arthritis that specifically inhibits COX-2.[12,13] Due to its COX-1 sparing activity, celecoxib appears to have a lower potential to produce upper GI ulcer complications than conventional

NSAIDs, based on the evidence accumulated to date. For example, celecoxib was shown to be associated with a four-fold to six-fold lower potential to produce gastroduodenal ulceration, as determined by endoscopy, than either naproxen or diclofenac; in these studies, the risk of gastroduodenal ulceration due to celecoxib was comparable to placebo.[14,15] More recently, a pooled analysis of 14 randomized controlled trials studies indicated that the incidence of upper GI ulcer complications associated with celecoxib use was eight-fold lower than that associated with NSAID (ibuprofen, diclofenac, or naproxen) treatment.[16] While promising, these results alone are inconclusive, and demonstration of a superior upper GI safety profile could only be clearly established by a large, long-term, prospective outcomes trial.

We report herein the results obtained from two companion, prospective, randomized, double-blind studies designed to assess the incidence of clinically significant upper GI ulcer complications among patients chronically receiving celecoxib or NSAIDs. To clearly establish that celecoxib is COX-1 sparing at doses that provide maximal COX-2 inhibition and efficacy, celecoxib administered at twice the maximum anti-inflammatory dose was compared to therapeutic doses of ibuprofen and diclofenac, two non-specific NSAIDs commonly used to treat OA and RA.

PATIENTS AND METHODS

Study Design

Two companion multicenter studies were simultaneously conducted at XX centers in the U.S. and Canada from December 1998 to December 1999. Each study was a double-blind, double-dummy, randomized, parallel trial. The companion studies were prospectively designed with the intent to pool the data into a single integrated analysis. This design was chosen to obviate concerns with patient compliance for taking study medication. Fully masking all treatment regimens in one trial, so that patients received the same number of capsules and all regimens were identical in appearance, would have required each patient to take 11 capsules per day. The companion studies were performed in accordance with the principles of good clinical practice and the Declaration of Helsinki. The trial protocols and amendments were reviewed and approved by the appropriate ethics committee and institutional review board at each study site, and written informed consent was obtained from each subject.

Study Population

Male and female outpatients 18 years of age and older were enrolled. Patients were eligible to participate if they were diagnosed with OA or RA evident for 3 months or longer and were expected to require continuous treatment with an NSAID for the duration of the trial.

Patients were excluded from the study if they had active GI tract, renal, hepatic, or coagulation disorders; malignancy (individuals who had been treated for basal cell carcinoma or who had a malignancy surgically removed with no recurrence within 5 years were not excluded); esophageal or gastroduodenal ulceration within the previous 30 days; a history of gastric or

duodenal surgery other than an oversew; or known hypersensitivity to COX-2 inhibitors, sulfonamides, ibuprofen, or diclofenac. Patients were also excluded from the studies if they had any clinically abnormal values on pretreatment laboratory tests as judged by the investigator. Women of childbearing age were excluded if they were pregnant, might become pregnant, or were lactating.

Study Protocol

Prior to enrollment, patients completed a physical examination and clinical laboratory testing, including a baseline serological test for *Helicobacter pylori* antibodies (FlexSure, Beckman-Coulter, Palo Alto, CA). Screening or baseline clinical assessments of arthritis included patient's global assessment of arthritis, scored on a scale of 1 (very good) to 5 (very poor), and the patient's assessment of arthritis pain, marked on a visual analog scale (VAS) from 0 mm (no pain) to 100 mm (most severe pain).

Patients were not required to undergo a washout period of NSAID before study entry. After discontinuing their current NSAID use, patients were allocated to one of the two companion studies. In each study, patients were randomly assigned to receive either celecoxib 400 mg BID or the comparator NSAID (ibuprofen 800 mg TID or diclofenac 75 mg BID). All treatment regimens were fully masked to ensure that all patients took the same number of capsules and that the two regimens in a single study were identical in appearance.

Follow-up visits took place at 4, 13, 26, 29, and 52 weeks after the initial dose of medication; an additional follow-up visit occurred at week 65 for the celecoxib and ibuprofen comparison

study. Arthritis assessments and clinical laboratory testing were repeated at all follow-up visits (fecal occult blood testing was repeated at the final visit only). Pregnancy testing was performed at weeks 13, 26, 39, and 52 (and week 65 for the celecoxib and ibuprofen comparison study). The SF-36 Health Survey and HAQ were repeated at week 26 and the final visit. Gastrointestinal and overall tolerability were based on clinical laboratory tests, physical examinations, observed or repeated adverse events, and withdrawals because of adverse events.

Concomitant Medications

Use of the following drugs was prohibited during the course of the study: NSAIDs (except for stables doses of aspirin up to 325 mg/d); anti-ulcer drugs (except for antacid use up to 7 days); antibiotics used alone or in combination with omeprazole, lansoprazole, and ranitidine for treatment of *H. pylori* infection; and antineoplastics. Use of oral, intramuscular, and intra-articular corticosteroids as well as daily use of calcium-containing antacids as a calcium supplement were permitted.

Outcome Measures

The primary end point was the incidence of upper GI ulcer complications during the period of drug administration (up to 65 weeks). Clinically significant upper GI ulcer complications were prospectively defined as follows:

1. Upper GI bleeding

- hematemesis with a lesion (ulcer or large erosion) at endoscopy or x-ray

- lesion (ulcer or large erosion) at endoscopy with evidence of active bleeding or stigmata of a recent hemorrhage (visible vessel or clot attached to the base of an ulcer)
- melena with a lesion (ulcer or large erosion) at endoscopy or x-ray with evidence of serious bleeding, which included at least one of the following:
    - decrease in hematocrit (of at least 5 percentage points) or decrease in hemoglobin (greater than 1.5 g/dL relative to baseline)
    - signs of postural vital sign changes (increase in pulse rate of at least 20 bpm and/or decrease in systolic blood pressure of at least 20 mm Hg and/or in diastolic blood pressure of at least 10 mm Hg)
    - transfusion of more than two units of blood
    - blood in the stomach at endoscopy or nasogastric aspiration

2. Perforation

This was defined as a perforated lesion that required surgery. It could involve a laparoscopic repair, but only if evidence of the perforation was unequivocal, such as free air in the abdomen visible by x-ray, or peritoneal signs upon physical examination.

3. Gastric outlet obstruction

Gastric outlet obstruction was required to be diagnosed by the investigator, and the diagnosis was required to be supported by endoscopy (e.g., ulcer with a tight edematous pyloric channel) or by x-ray results (e.g., a dilated stomach, delayed barium emptying with clinical evidence of outlet obstruction and with an ulcer in the channel, or severe outlet narrowing and edema)

Investigators were instructed to identify and report all potential clinically significant upper GI ulcer complications. A complete evaluation was required for any of the following presentations: severe acute abdominal pain or acute abdomen; intractable abdominal pain with nausea or vomiting; hematemesis or melena; acute hypovolemia or hypotension; history of melena within past 14 days or black stool representing a change in normal pattern; development of postural dizziness or lightheadedness, or syncope; history of vaguely characterized dark stool, or dark stool within past 14 days or with concurrent iron or bismuth ingestion; history of hematochezia, or anal or rectal bleeding after elimination; development of new anemia or decrease in hematocrit of 5% of more; development of dyspepsia, abdominal pain, or nausea or vomiting; or development of heme-positive stools.

All potential clinically significant upper GI ulcer complications were evaluated according to a pre-specified algorithm. If evidence of a potential upper GI ulcer complication was lacking, the event was classified as an unspecified event. If evidence of a potential upper GI ulcer complication was present, all documentation relating to the event was forwarded to a Gastrointestinal Events Committee (GEC; comprised of Jay Goldstein, MD, Naurang Agrawal, MD, Glenn Eisen, MD, and William Stenson, MD), which was established to review and adjudicate all potential upper GI ulcer complications. Reviews of all events by the GEC were conducted in a blinded fashion. The GEC collectively reviewed each case and assigned it by consensus as either meeting or not meeting the definition of a clinically significant upper GI ulcer complication.

In addition to clinically significant upper GI ulcer complications, data were collected on other GI adverse events, including symptomatic upper GI ulcers and lower GI adverse events.

Statistical Analysis

The sample size calculations were based on the assumption that the annualized incidence of upper GI ulcer complications would be 0.3% for celecoxib and 1.2% for each NSAID. To detect this difference with a 5% significance level (two-sided) and a power of 85% and assuming a 30% withdrawal rate, a sample size of 4,000 patients was required for the celecoxib group and 2,000 patients for each NSAID group. A total of 40 clinically significant ulcer complications were expected from both studies. The studies were scheduled to conclude when 20 adjudicated events had been obtained from each study or a total of 45 events had been obtained from the two studies combined.

Homogeneity of the treatment groups at baseline was analyzed by using the chi-square test for categorical variables and two-way ANOVA with treatment and center effects for continuous variables.

All analyses of safety were based on intent-to-treat populations, which consisted of all subjects who received at least one dose of assigned study medication. In the primary outcome analysis, time-to-event analyses of upper GI ulcer complications were performed based on Kaplan-Meier estimates of cumulative even incidences. Log-rank tests were used to compare the incidences.

Potential risk factors for the development of an ulcer complication were identified prior to the study. These included demographic and disease characteristics (age; disease type and duration; baseline disease severity; and GI history, such as positive *H. pylori* serology, history of upper GI bleeding or gastroduodenal ulcer, or NSAID intolerance), history of cardiovascular disease, concomitant medication use, alcohol use, or tobacco use. Each of these factors was analyzed by univariate logistic regression analysis.

Upper GI ulcer complications not considered to be possibly related to the study drug were censored in the following manner. Events occurring within 48 hours after midnight of the first dose day or more than 48 hours after midnight of the last dose day were censored and not included in the analysis. However, any of the latter events were included in the analysis if they occurred within two weeks after the last dose of study medication and were considered by the GEC to be related to treatment.

RESULTS

A total of XX patients were enrolled in the two companion studies (Figure 1). XX patients were randomly assigned to receive celecoxib. XX patients received NSAIDs; of these, XX were randomly allocated to ibuprofen and XX to diclofenac. In the two studies combined, XX% (XX patients) had OA, while XX% (XX patients) had RA (Table 1). At baseline, no significant differences were detected among the treatment groups with respect to demography, duration of OA or RA, history of GI disease and disease severity, or NSAID intolerance. (1) The studies were completed by XX patients (XX%). Withdrawal rates were similar for all treatment groups. XX% (XX patients) of celecoxib-treated patients withdrew from the study in comparison to XX% (XX patients) and XX% (XX patients) for the ibuprofen and diclofenac groups, respectively. Reasons for early discontinuation are summarized in Figure 1. (2) The studies were completed by XX patients (XX%). As shown in Figure 1, the most common cause(s) of withdrawal was XX. Approximately XX-fold fewer celecoxib-treated patients (XX%, XX patients) withdrew for this reason in comparison to patients in the ibuprofen (XX%, XX patients) and diclofenac (XX%, XX patients) groups.

A total of XX potential clinically significant upper GI ulcer complications were reported (Table 2). Of these, the GEC identified and adjudicated XX bleeding episodes, XX gastric outlet obstructions, and XX perforations (Figure 2; Table 3); upper GI bleeding, gastric outlet obstruction, and perforation were most frequently detected in the XX, XX, and XX, respectively. For patients receiving NSAIDs, upper GI ulcer complications occurred in XX (XX%) ibuprofen-treated patients and in XX (XX%) diclofenac-treated patients. The combined incidence of upper GI ulcer complications for the NSAID group was approximately

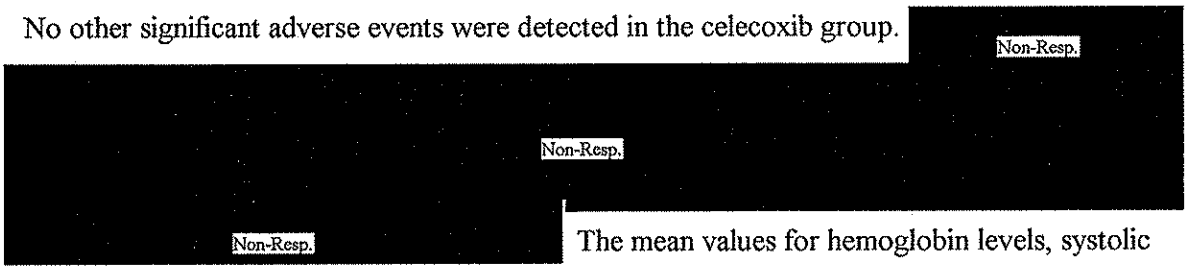
XX%. In comparison, upper GI ulcer complications were identified in XX (XX%) of patients receiving celecoxib. When normalized according to patient-years of exposure, the annualized incidences of upper GI ulcer complications were XX%, XX%, and XX% for celecoxib, ibuprofen, and diclofenac, respectively. Overall, the risk of developing a clinically significant upper GI ulcer complication was XX-fold lower in the celecoxib group than in either NSAID group. The time-to-event analysis also demonstrated a difference in favor of celecoxib versus ibuprofen or diclofenac (Figure 3). (1) Upper GI ulcer complications were more frequently detected in patients over the age of 65/with a history of XX/who were concurrently receiving XX (XX%, XX patients) than in patients under the age of 65/without a history of XX/who were not concurrently receiving XX (XX%, XX patients) (Table 4). (2) An analysis of previously identified risk factors for NSAID-induced ulcer complications did not reveal an effect of any of these factors on the incidence of upper GI ulcer complications in our investigation (Table 4).

Although the dose of celecoxib used in the trial was twice the maximum anti-inflammatory dose, celecoxib 400 mg BID was safe and well tolerated when chronically administered. The incidence rate for all adverse events combined and the 5 most common adverse events are listed in Table 5. During the course of the study, the incidence of overall adverse events was significantly higher in the NSAID treatment groups relative to the celecoxib group; XX (XX%) celecoxib-treated patients, XX (XX%) ibuprofen-treated patients, and XX (XX%) diclofenac-treated patients reported adverse events, respectively. Fewer celecoxib-treated patients (XX%, XX patients) withdrew from the studies due to adverse events than patients in either NSAID group (XX%, XX patients for ibuprofen and XX%, XX patients for diclofenac). The 9-month

cumulative incidences of study withdrawals due to adverse events were XX% (XX patients) for the celecoxib group, XX% (XX patients) for the ibuprofen group, and XX% (XX patients) for the diclofenac group. By 12 months, XX% (XX patients) of the celecoxib group had withdrawn from the study, while XX% (XX patients) and XX% (XX patients) of the ibuprofen and diclofenac groups had withdrawn, respectively. The difference between the celecoxib group and each NSAID group was significant.

GI-related adverse events constituted XX% (XX of XX) of all adverse events (Table 5). The frequency of GI-related adverse events was approximately XX-fold lower in the celecoxib group (XX%, XX patients) than in the ibuprofen group (XX%, XX patients) or diclofenac group (XX%, XX patients). Consistent with earlier reports, the incidence of gastroduodenal ulcers was lower in the celecoxib group (XX%, XX patients) than in the ibuprofen (XX%, XX patients) or diclofenac (XX%, XX patients) group.

No other significant adverse events were detected in the celecoxib group.



The mean values for hemoglobin levels, systolic and diastolic blood pressures, creatine levels, or activity of hepatic enzymes, such as alanine aminotransferase and aspartate aminotransferase, were not significantly altered in the celecoxib group (Table 6).

All treatment regimens improved the pain and inflammation due to OA and RA to comparable degrees as determined by all measures of efficacy (data not shown). The number of patients withdrawn due to lack of treatment efficacy was similar for each treatment group; XX% (XX patients) of the celecoxib group, XX% (XX patients) of the ibuprofen group, and XX% (XX patients) of the diclofenac group withdrew, respectively. Data relating to efficacy and quality of life assessments performed in this study have been described elsewhere.

DISCUSSION

We have presented here the results of two companion studies comparing the effects of celecoxib, a COX-2-specific inhibitor, and two non-specific NSAIDs on the incidence of upper GI ulcer complications in OA and RA patients. Our results demonstrate that long-term use of celecoxib, even when administered at a supratherapeutic dose, is associated with a significantly lower frequency of upper GI ulcer complications than long-term use of either ibuprofen or diclofenac provided at a therapeutic dose. The annualized incidence of upper GI ulcer complications was XX% for patients receiving celecoxib, and XX% and XX% for patients receiving ibuprofen and diclofenac, respectively. Overall, the risk of developing an upper GI ulcer complication was XX-fold to XX-fold greater for NSAID-treated patients than for celecoxib-treated patients. Altogether, these data indicate that celecoxib has superior upper GI safety relative to diclofenac and ibuprofen in both OA and RA patients.

Our investigation is distinguished from the majority of studies that have examined the association between NSAIDs and upper GI toxicity. Such studies have primarily been retrospective epidemiological case-control or cohort analyses that tested the association of NSAIDs to GI-related hospitalizations for upper GI bleeding or perforation. Instead, we chose to use routine clinical criteria to define clinically significant upper GI complications. Despite this methodological difference, the XX% annualized rate with NSAIDs observed in our study is in reasonable agreement with/only slightly higher than, for example, the 0.9% to 1.3% annual rates of GI-related hospitalizations due to NSAID use derived from certain epidemiological studies.[3,17]

The XX% annualized incidence of NSAID-related ulcer complications is also consistent with incidences obtained from studies using similar pre-specified criteria. For instance, a 1.9% annual incidence of upper GI ulcer complications due to NSAID use was found in the MUCOSA study.[4] Similarly, other studies that examined the effect of selective COX-2 inhibition on the development of upper GI ulcer complications reported an annualized incidence of 1.68% to 1.8%.[16,18] Based on these comparisons, it appears that our method of reviewing and adjudicating upper GI ulcer complications was sensitive and reliable.

While gastroduodenal ulcers detected by upper GI endoscopy have been considered by some as surrogate markers for upper GI ulcer complications, their reliability as antecedents to NSAID-induced upper GI ulcer complications has been questioned, given that endoscopic ulcers can be identified in over 20% of NSAID users and that significant upper GI ulcer complications may occur without prior evidence of mucosal damage.[19,20,21,22,23] Interestingly, we observed that the relative reductions in the rates of gastroduodenal ulcers confirmed by endoscopy or x-ray (XX%) and upper GI ulcer complications (XX%) in celecoxib-treated patients were in reasonably good agreement. Another indicator that has been used for upper GI ulcer complications is a composite end point consisting of upper GI perforation, ulceration, and bleeding (PUB).[18] In this regard, it has been suggested that this approach is also limited, since it combines commonly occurring ulcers with much less frequently occurring perforations and bleeding.[24] Rather, a composite end point comprised of upper GI perforation, obstruction, and bleeding, such as the one used in the present analysis, may be a more accurate indicator of clinically significant upper GI ulcer complications.

We also chose to compare celecoxib against more than one NSAID, since it had been previously reported that individual NSAIDs can produce varying degrees of upper GI toxicity.[25] Ibuprofen and diclofenac were selected as comparators because these NSAIDs are generally associated with the lowest frequencies of upper GI ulcer complications.[26] Since our data show that celecoxib has a lower potential than either ibuprofen or diclofenac for producing upper GI ulcer complications, it is reasonable to conclude that celecoxib is most likely superior to all NSAIDs in terms of upper GI safety.

Given the patient population selected for the study and the necessity for a chronic treatment period, it was not possible to include a placebo arm in the trial. However, historical data indicate that the annualized incidence of upper GI ulcer complications for celecoxib reported here is comparable to previously published incidences, which ranged from 0% to 0.9%, for patients of reasonably similar demography and medical history who were not taking NSAIDs.[3,16,17,18] Therefore, it is plausible that the risk of upper GI ulcer complications associated with long-term use of celecoxib may be similar to the background incidence in non-treated patients.

Advanced age has been identified as one of the primary risk factors for NSAID-induced ulcer complications. Many studies have also identified one or more of the following risk factors: higher doses, history of upper GI injury (e.g., gastroduodenal ulceration and upper GI bleeding), concomitant corticosteroid use, concomitant anticoagulant use, and a history of cardiovascular disease.[27,28] (1) Our results confirm previous findings. Patients over the age of 65/with a history of XX/who were concurrently taking XX had a XX-fold greater risk of

experiencing an upper GI ulcer complication. (2) The precise cause(s) the ulcer complications that developed in patients treated with celecoxib in our study are not readily apparent. Age, disease type and duration, history of GI disease, history of cardiovascular disease, *H. pylori* status, concurrent medication use, alcohol use, and tobacco use did not appear to predispose to upper GI ulcer complications in our study.

NSAID-related GI toxicity ranges in severity from life-threatening ulcer complications to asymptomatic ulcers or side effects, such as abdominal pain, dyspepsia, and nausea. Our data indicate that the occurrence of GI-related adverse events was lower in the celecoxib group (XX%) than in either the ibuprofen (XX%) or diclofenac (XX%) group; the incidence of other untoward effects, such as renal and hepatic effects, was not significant. Notably, this rate is similar to the withdrawal rates associated with celecoxib use in studies of substantially shorter duration.[14,15,29] It appears then that celecoxib is generally well tolerated even with long-term use. Considering that it has been estimated that approximately 20% to 30% of patients receiving NSAIDs develop peristent GI-related adverse events and that as many as 10% discontinue treatment because of these symptoms,[3,30] our findings may have important implications on improving treatment compliance in OA and RA patients.

In the present study, celecoxib relieved the pain and inflammation due to OA and RA as effectively as both ibuprofen and diclofenac. The reduction in pain was meaningful to patients in all treatment groups as assessed by the SF-36 Health Survey and the HAQ. These findings, in conjunction with the above results, indicate that celecoxib provides sustained arthritis efficacy without detrimental effects on GI safety and tolerability.

Based on our findings, we conclude that long-term use of celecoxib is associated with a significantly lower risk of clinically significant upper GI ulcer complications than long-term use of either ibuprofen or diclofenac. Overall, our analysis indicates that celecoxib can reduce the risk of mild to life-threatening NSAID-mediated upper GI tract injury when used chronically for the treatment of OA or RA.

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Table 1. Baseline Characteristics and Patient Demographics

Characteristic	Celecoxib 400 mg BID (n = XX)	Ibuprofen 800 mg TID (n = XX)	Diclofenac 75 mg BID (n = XX)
Mean age, y (range)			
Gender, n (%) Male Female			
Race, n (%) White Black Asian Hispanic Other			
Primary disease, n (%) OA RA			
Mean duration of disease, y OA RA			
History of GI bleeding, n (%)			
History of gastroduodenal ulcer, n (%)			
History of GI-related NSAID intolerance, n (%)			

Concurrent medications, n (%)			
Aspirin			
Corticosteroids			
DMARDs			

Table 2. Incidence of Potential Clinically Significant upper GI Ulcer Complications

Category	Celecoxib 400 mg BID (n = XX)	Ibuprofen 800 mg TID (n = XX)	Diclofenac 75 mg BID (n = XX)
Total potential ulcer complications			
Not meeting definition of a complication Anemia Esophageal stricture/ esophagitis/erosive esophagitis/ulcerative esophagitis/esophageal ulcer/esophageal carcinoma GERD Gastric arteriovenous malformations Mallory-Weiss tear Gastritis/erosive gastritis/ duodenitis Uncomplicated gastric ulcer/ pyloric channel ulcer/ gastroduodenal ulcer/ duodenal ulcer/ Small bowel obstruction Diverticulosis/diverticulitis/ diverticular bleeding Colitis/ischemic colitis/ colonic polyps/			

colon carcinoma			
Hemorrhoids/proctitis			
Cholelithiasis			
Total definite ulcer complications			

Table 3a. Incidence of Definite Clinically Significant upper GI Ulcer Complications (w/ *P* values)

Category	Celecoxib 400 mg BID (n = XX)	Ibuprofen 800 mg TID (n = XX)	Diclofenac 75 mg BID (n = XX)	Celecoxib vs. Ibuprofen	Celecoxib vs. Diclofenac
	← n (%) →			← *P* value →	
Total upper GI ulcer complications					
Hematemesis with a lesion					
Lesion with evidence of active bleeding or stigmata of recent hemorrhage					
Melena with a lesion					
Hemoccult-positive stool with a lesion and a decrease in hematocrit of >5%					
Hemoccult-positive stool with a lesion and signs of postural hypotension					
Hemoccult-positive stool with a lesion and a need for 2 units of blood transfusion					
Hemoccult-positive stool with a lesion and blood in stomach					
Perforated ulcer					
Gastric outlet obstruction					
Total patient-years of exposure					
Annualized incidence					

Table 3b. Incidence of Definite Clinically Significant upper GI Ulcer Complications (w/o *P* values)

Category	Celecoxib 400 mg BID (n = XX)	Ibuprofen 800 mg TID (n = XX)	Diclofenac 75 mg BID (n = XX)
	← n (%) →		
Total upper GI ulcer complications Hematemesis with a lesion Lesion with evidence of active bleeding or stigmata of recent hemorrhage Melena with a lesion Hemoccult-positive stool with a lesion and a decrease in hematocrit of >5% Hemoccult-positive stool with a lesion and signs of postural hypotension Hemoccult-positive stool with a lesion and a need for 2 units of blood transfusion Hemoccult-positive stool with a lesion and blood in stomach Perforated ulcer Gastric outlet obstruction			
Total patient-years of exposure			
Annualized incidence			

Table 4. Risk Factor Analysis

Category	Celecoxib 400 mg BID (n = XX)	Ibuprofen 800 mg TID (n = XX)	Diclofenac 75 mg BID (n = XX)	Celecoxib vs. Ibuprofen	Celecoxib vs. Diclofenac
	← n (%) →			← *P* value →	
Age <=65 years > 65 years					
Primary disease OA RA					
Duration of OA < 5 years >= 5 years					
Duration of RA < 5 years >= 5 years					
History of upper GI bleeding Positive Negative					
History of gastroduodenal ulcer Positive Negative					
History of GI-related NSAID intolerance Positive Negative					
Helicobacter pylori status					

Positive					
Negative					
Concomitant aspirin use					
Positive					
Negative					
Concomitant corticosteroid use					
Positive					
Negative					
Concomitant DMARD use					
Positive					
Negative					
Tobacco use					
Positive					
Negative					
Alcohol use					
Positive					
Negative					

Table 5a. Incidence of Adverse Events (w/ *P* values)

Category	Celecoxib 400 mg BID (n = XX)	Ibuprofen 800 mg TID (n = XX)	Diclofenac 75 mg BID (n = XX)	Celecoxib vs. Ibuprofen	Celecoxib vs. Diclofenac
	← n (%) →			← *P* value →	
Adverse events Total Causing withdrawal					
Most frequent adverse events XX XX XX XX XX					
GI adverse events Gastric ulcer Duodenal ulcer XX XX XX					
Renal adverse events Peripheral edema [redacted] Non-Resp					

Table 5b. Incidence of Adverse Events (w/o *P* values)

Category	Celecoxib 400 mg BID (n = XX)	Ibuprofen 800 mg TID (n = XX)	Diclofenac 75 mg BID (n = XX)
	n (%)		
Adverse events			
Total			
Causing withdrawal			
Most frequent adverse events			
XX			
XX			
XX			
XX			
GI adverse events			
Gastric ulcer			
Duodenal ulcer			
XX			
XX			
XX			
Renal adverse events			
Peripheral edema			

Non-Respl

Table 6. Representative Clinical Laboratory Measurements

Measurement	Celecoxib 400 mg BID (n = XX)	Ibuprofen 800 mg TID (n = XX)	Diclofenac 75 mg BID (n = XX)
Blood pessure, mm Hg Systolic Baseline Final vsit Diastolic Baseline Final vsit			
Hemoglobin, g/L Baseline Final visit			
Creatine, µmol/L Baseline Final visit			
Alanine aminotransferase, U/L Baseline Final visit			
Aspartate aminotransferase, U/L Baseline Final visit			

Figure 1. Patient Disposition Flowchart

Figure 2. Incidence of Clinically Significant upper GI Ulcer Complications

(Bar graph: X axis = Total no. upper GI events; Y axis = Celecoxib, Ibuprofen, and Diclofenac)

Figure 3. Time-to-Event Analysis for Clinically Significant upper GI Ulcer Complications

(Kaplan-Meier curves for celecoxib, ibuprofen, and diclofenac)

EXHIBIT 149

THE CELECOXIB LONG-TERM ARTHRITIS SAFETY STUDY (CLASS)

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From

Running Title: GI Safety of Celecoxib

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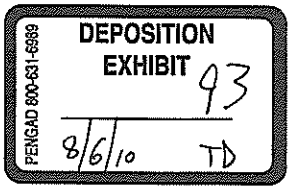

ABSTRACT

Context: Use of nonsteroidal anti-inflammatory drugs (NSAIDs) is associated with symptomatic upper gastrointestinal (GI) ulcers and ulcer complications such as perforation, obstruction and bleeding. These effects have been linked to inhibition of cyclooxygenase (COX)-1 and loss of prostaglandin-dependent mucosal protection. Celecoxib specifically inhibits COX-2 and has demonstrated a low potential for producing GI injury.

Objective: To compare the incidence of symptomatic ulcers and ulcer complications in patients with osteoarthritis (OA) or rheumatoid arthritis (RA) treated with twice the highest recommended dose of celecoxib versus two NSAID comparators administered at standard therapeutic doses.

Design: Randomized, multicenter, double-blind trial lasting 6 months with follow-up visits occurring at weeks 4, 13 and 26 from December 1998 through January 2000.

Setting: Three hundred eighty clinical sites in the United States and Canada.

Patients: A total of 7,982 patients aged 18 years and older with OA (n= 5,795) or RA (n= 2,187) who met inclusion criteria were randomized; 4,575 (57%) patients completed the study.

Interventions: Patients were randomized to receive celecoxib 400 mg twice daily (n=3,995) versus ibuprofen 800 mg three times per day (n=1,988) and diclofenac 75 mg twice daily (n=1,999) (combined).

Main Outcome Measures: Cumulative incidence of symptomatic ulcers and ulcer complications combined or ulcer complications alone for celecoxib versus NSAIDs based on survival analysis of time to event using symptomatic ulcers and ulcer complications that met pre-specified criteria judged by a blinded expert adjudication committee.

Results: The incidence of symptomatic ulcers and ulcer complications over 6 months was significantly lower with celecoxib compared to NSAIDs (annualized incidence 2.0% vs 3.5%, p=0.023; relative risk = 0.57; 95% confidence interval 0.xx to 0.xx). This treatment effect was further evident when patients taking low dose aspirin (≤325 mg daily; n=) for cardiovascular prophylaxis were excluded (annualized incidence 1.5% vs 3.0%, p=0.017; relative risk = 0.50; 95% confidence interval 0.xx to 0.xx). The annualized incidence rates of ulcer complications alone for celecoxib and NSAIDs were 0.75% and 1.45%, respectively (p=0.092) and 0.45% and 1.3%, respectively in non-aspirin users (p=0.047; relative risk = 0.35; 95% confidence interval 0.xx to 0.xx). Overall, celecoxib was also better tolerated than NSAIDs as fewer celecoxib-treated patients experienced GI, hepatic and renal or bleeding-related adverse effects.

Conclusion: At twice the highest therapeutic dose, chronic use of celecoxib was associated with a significantly lower incidence of symptomatic ulcers and ulcer complications and improved general safety and tolerability than therapeutic doses of NSAIDs. This study establishes that celecoxib has a low potential for producing GI injury and has other significant benefits when used chronically for the treatment of OA or RA.

Key words: ulcer complications, symptomatic ulcers, bleeding, NSAIDs, celecoxib

Word count: 429/250

INTRODUCTION

It is estimated that 13 to 15 million patients with osteoarthritis (OA) and rheumatoid arthritis (RA) in the United States require regular and often chronic treatment with nonsteroidal anti-inflammatory drugs (NSAIDs).[1,2] A well-established limitation of NSAID therapy is the risk of developing clinically significant injury to the upper gastrointestinal (GI) tract, including ulceration or an ulcer complication such as perforation, gastric outlet obstruction and hemorrhage.[3,4] Based on epidemiological and controlled trial experience, there is an estimated five-to ten-fold greater risk for developing a symptomatic ulcer or ulcer complication in NSAID users when compared to nonusers and an annual incidence rate ranging from 2-4% or 1-2% for ulcer complications alone.[3,4]

NSAIDs inhibit cyclooxygenase (COX), the enzyme that converts arachidonic acid to prostaglandins and ulcerogenic effects of these agents are attributed to interference with prostaglandin production and mucosal protection in the upper GI tract. COX exists in two isoforms.[5-7] COX-1 is a ubiquitous constitutive isozyme; gastrointestinal prostaglandins and thromboxane A_2 formed in platelets are derived exclusively from COX-1.[10] COX-2 is largely a cytokine-induced isozyme, produces prostaglandins that mediate pain and inflammation.[11-13] With the exception of brain, reproductive organs and kidney, COX-2 is expressed in very low levels in most normal tissue, but is up-regulated in inflammatory cells such as activated macrophages and synoviocytes.[12,14,15] All NSAIDs inhibit both COX-1 and COX-2, each to varying degrees.[16-18] Thus, the therapeutic effects of NSAIDs are derived from their ability to inhibit COX-2 activity, while the adverse effects of these agents within the upper GI tract or platelet function arise from inhibition of COX-1 function.

Celecoxib (Celebrex) is a recently approved agent for treating the inflammation and pain of arthritis that specifically inhibits COX-2.[5,6] Celecoxib appears to have a little potential to produce upper GI injury as evidenced by a four-fold to six-fold lower association with gastroduodenal ulceration, as determined by endoscopy, than either naproxen or diclofenac. In these studies, the risk of gastroduodenal ulceration in celecoxib-treated patients was comparable to placebo.[7,8] More recently, a pooled analysis of 14 randomized controlled trials studies indicated that the incidence of upper GI ulcer complications associated with celecoxib use was eight-fold lower than that associated with diclofenac, ibuprofen and naproxen combined.[9]

While promising, these results alone are inconclusive, and the demonstration of a superior upper GI safety could only be clearly established by a large, long-term, prospective outcomes trial. We report here the results obtained from a prospective, randomized, double-blind study designed to assess the incidence of symptomatic ulcers and ulcer complications among OA and RA patients chronically receiving celecoxib or NSAIDs. To clearly establish that celecoxib is COX-1 sparing at doses that provide maximal COX-2 inhibition and efficacy, celecoxib administered at twice the maximum anti-inflammatory dose was compared to therapeutic doses of ibuprofen and diclofenac, two non-specific NSAIDs commonly used to treat OA and RA.

METHODS

Study Population

Men and women outpatients 18 years of age and older were eligible to participate in the study they were diagnosed with OA or RA evident for 3 months or longer and were expected to require continuous treatment with an NSAID for the duration of the trial. Patients were excluded from the study participation if they had active GI, renal, hepatic, or coagulation disorders; malignancy (unless removed surgically with no recurrence within 5 years); esophageal or gastroduodenal ulceration within the previous 30 days; a history of gastric or duodenal surgery other than an oversew; or known hypersensitivity to COX-2 inhibitors, sulfonamides, ibuprofen, or diclofenac. Women were excluded if they were pregnant, might become pregnant, or were lactating.

Study Protocol

This prospective, randomized, double-blind trial was conducted at 380 centers in the United States and Canada from December 1998 to January 2000 in accordance with the principles of good clinical practice and the Declaration of Helsinki. The protocol was approved by the institutional review board at each study site and all patients were required to provide written informed consent.

Prior to enrollment, patients completed a physical examination and clinical laboratory testing, including a baseline serological test for *Helicobacter pylori* antibodies (FlexSure, Beckman-Coulter, Palo Alto, CA). Screening or baseline clinical assessments of arthritis included patient's global assessment of arthritis, scored on a scale of 1 (very good) to 5 (very poor), and

the patient's assessment of arthritis pain, marked on a visual analog scale (VAS) from 0 mm (no pain) to 100 mm (most severe pain). Follow-up clinic visits took place at weeks 4, 13, and 26 after the initial dose of medication. Arthritis assessments and clinical laboratory testing were repeated at all follow-up visits.

Treatment

Patients were randomly assigned by a computer-generated randomization schedule to receive either celecoxib 400 mg BID or the comparator NSAID (ibuprofen 800 mg TID or diclofenac 75 mg BID). All treatment regimens were fully masked to ensure they were identical in appearance and that patients took the same number of capsules.

Concomitant Medications

NSAIDs (except for stables doses of aspirin up to 325 mg/d); anti-ulcer drugs (except for antacid use up to 7 days); antibiotics used alone or in combination with omeprazole, lansoprazole, and ranitidine for treatment of *H. pylori* infection; and antineoplastics were prohibited during the course of the study. Use of oral, intramuscular, and intra-articular corticosteroids, DMARDs, as well as daily use of calcium-containing antacids as a calcium supplement were permitted.

Clinical Assessments

Investigators were instructed to identify and report all potential ulcer complications. A complete evaluation according to a pre-specified algorithm was required for any of the following presentations: severe acute abdominal pain or acute abdomen; intractable abdominal

pain with nausea or vomiting; hematemesis or melena; acute hypovolemia or hypotension; history of melena within past 14 days or black stool representing a change in normal pattern; development of postural dizziness or lightheadedness, or syncope; history of vaguely characterized dark stool, or dark stool within past 14 days or with concurrent iron or bismuth ingestion; history of hematochezia, or anal or rectal bleeding after elimination; development of new anemia or decrease in hematocrit of 5% of more; development of dyspepsia, abdominal pain, or nausea or vomiting; or development of heme-positive stools.

All documentation relating to potential ulcer complications was forwarded to a Gastrointestinal Events Committee (comprised of Jay Goldstein, MD, Naurang Agrawal, MD, Glenn Eisen, MD, and William Stenson, MD). The Committee was established to review and adjudicate all potential events according to prospectively established ulcer complication definitions as provided in Table 1. The Committee collectively reviewed each case in a blinded fashion and assigned it by consensus as either meeting or not meeting the definition of an ulcer complication. Symptomatic ulcers comprised those cases that did not meet the definition of an ulcer complication, but did have endoscopic or x-ray evidence of a gastric or duodenal ulcer as judged by the Committee.

Statistical Analysis

The sample size calculations were based on the assumption that the annualized incidence of upper GI ulcer complications would be 0.3% for celecoxib and 1.2% for NSAIDs. To detect this difference with a 5% significance level (two-sided) and a power of 85% and assuming a

30% withdrawal rate, a sample size of 4,000 patients was required for the celecoxib group and 2,000 patients for each NSAID group.

Homogeneity of the treatment groups at baseline was analyzed by using the chi-square test for categorical variables and two-way ANOVA with treatment and center effects for continuous variables. All statistical analyses were conducted on the intent-to-treat populations which consisted of all patients who received at least one dose of assigned study medication. Time-to-event analyses of ulcers plus upper GI ulcer complications or ulcer complications alone were performed based on Kaplan-Meier estimates of cumulative event rates. Log-rank tests were used to compare the incidence rates. Potential risk factors for the development of an ulcer complication were pre-specified and analyzed by univariate logistic regression analysis. Treatment-related differences in the incidence of adverse effects or clinical laboratory changes were determined by Fisher's exact test.

RESULTS

A total of 3,995 patients received celecoxib 400 mg BID patients received NSAIDs; of these, XX were randomly allocated to ibuprofen and XX to diclofenac. In the two studies combined, XX% (XX patients) had OA, while XX% (XX patients) had RA (Table 1). At baseline, no significant differences were detected among the treatment groups with respect to demography, duration of OA or RA, history of GI disease and disease severity, or NSAID intolerance. (1) The studies were completed by XX patients (XX%). Withdrawal rates were similar for all treatment groups. XX% (XX patients) of celecoxib-treated patients withdrew from the study in comparison to XX% (XX patients) and XX% (XX patients) for the ibuprofen and diclofenac groups, respectively. Reasons for early discontinuation are summarized in Figure 1. (2) The studies were completed by XX patients (XX%). As shown in Figure 1, the most common cause(s) of withdrawal was XX. Approximately XX-fold fewer celecoxib-treated patients (XX%, XX patients) withdrew for this reason in comparison to patients in the ibuprofen (XX%, XX patients) and diclofenac (XX%, XX patients) groups.

A total of XX potential clinically significant upper GI ulcer complications were reported (Table 2). Of these, the GEC identified and adjudicated XX bleeding episodes, XX gastric outlet obstructions, and XX perforations (Figure 2; Table 3); upper GI bleeding, gastric outlet obstruction, and perforation were most frequently detected in the XX, XX, and XX, respectively. For patients receiving NSAIDs, upper GI ulcer complications occurred in XX (XX%) ibuprofen-treated patients and in XX (XX%) diclofenac-treated patients. The combined incidence of upper GI ulcer complications for the NSAID group was approximately XX%. In comparison, upper GI ulcer complications were identified in XX (XX%) of patients

receiving celecoxib. When normalized according to patient-years of exposure, the annualized incidences of upper GI ulcer complications were XX%, XX%, and XX% for celecoxib, ibuprofen, and diclofenac, respectively. Overall, the risk of developing a clinically significant upper GI ulcer complication was XX-fold lower in the celecoxib group than in either NSAID group. The time-to-event analysis also demonstrated a difference in favor of celecoxib versus ibuprofen or diclofenac (Figure 3). (1) Upper GI ulcer complications were more frequently detected in patients over the age of 65/with a history of XX/who were concurrently receiving XX (XX%, XX patients) than in patients under the age of 65/without a history of XX/who were not concurrently receiving XX (XX%, XX patients) (Table 4). (2) An analysis of previously identified risk factors for NSAID-induced ulcer complications did not reveal an effect of any of these factors on the incidence of upper GI ulcer complications in our investigation (Table 4).

Although the dose of celecoxib used in the trial was twice the maximum anti-inflammatory dose, celecoxib 400 mg BID was safe and well tolerated when chronically administered. The incidence rate for all adverse events combined and the 5 most common adverse events are listed in Table 5. During the course of the study, the incidence of overall adverse events was significantly higher in the NSAID treatment groups relative to the celecoxib group; XX (XX%) celecoxib-treated patients, XX (XX%) ibuprofen-treated patients, and XX (XX%) diclofenac-treated patients reported adverse events, respectively. Fewer celecoxib-treated patients (XX%, XX patients) withdrew from the studies due to adverse events than patients in either NSAID group (XX%, XX patients for ibuprofen and XX%, XX patients for diclofenac). The 9-month cumulative incidences of study withdrawals due to adverse events were XX% (XX patients) for

the celecoxib group, XX% (XX patients) for the ibuprofen group, and XX% (XX patients) for the diclofenac group. By 12 months, XX% (XX patients) of the celecoxib group had withdrawn from the study, while XX% (XX patients) and XX% (XX patients) of the ibuprofen and diclofenac groups had withdrawn, respectively. The difference between the celecoxib group and each NSAID group was significant.

GI-related adverse events constituted XX% (XX of XX) of all adverse events (Table 5). The frequency of GI-related adverse events was approximately XX-fold lower in the celecoxib group (XX%, XX patients) than in the ibuprofen group (XX%, XX patients) or diclofenac group (XX%, XX patients). Consistent with earlier reports, the incidence of gastroduodenal ulcers was lower in the celecoxib group (XX%, XX patients) than in the ibuprofen (XX%, XX patients) or diclofenac (XX%, XX patients) group.

No other significant adverse events were detected in the celecoxib group. Renal effects, such as peripheral edema Non-Resp. occurred at a low frequency in celecoxib-treated patients (XX%, XX patients) relative to NSAID-treated patients (XX%, XX patients for ibuprofen; XX%, XX patients for diclofenac) (Table 5). Non-Resp.

Non-Resp.

Non-Resp. .

All treatment regimens improved the pain and inflammation due to OA and RA to comparable degrees as determined by all measures of efficacy (data not shown). The number of patients

withdrawn due to lack of treatment efficacy was similar for each treatment group; XX% (XX patients) of the celecoxib group, XX% (XX patients) of the ibuprofen group, and XX% (XX patients) of the diclofenac group withdrew, respectively. Data relating to efficacy and quality of life assessments performed in this study have been described elsewhere.

DISCUSSION

We have presented here the results of two companion studies comparing the effects of celecoxib, a COX-2-specific inhibitor, and two non-specific NSAIDs on the incidence of upper GI ulcer complications in OA and RA patients. Our results demonstrate that long-term use of celecoxib, even when administered at a supratherapeutic dose, is associated with a significantly lower frequency of upper GI ulcer complications than long-term use of either ibuprofen or diclofenac provided at a therapeutic dose. The annualized incidence of upper GI ulcer complications was XX% for patients receiving celecoxib, and XX% and XX% for patients receiving ibuprofen and diclofenac, respectively. Overall, the risk of developing an upper GI ulcer complication was XX-fold to XX-fold greater for NSAID-treated patients than for celecoxib-treated patients. Altogether, these data indicate that celecoxib has superior upper GI safety relative to diclofenac and ibuprofen in both OA and RA patients.

Our investigation is distinguished from the majority of studies that have examined the association between NSAIDs and upper GI toxicity. Such studies have primarily been retrospective epidemiological case-control or cohort analyses that tested the association of NSAIDs to GI-related hospitalizations for upper GI bleeding or perforation. Instead, we chose to use routine clinical criteria to define clinically significant upper GI complications. Despite this methodological difference, the XX% annualized rate with NSAIDs observed in our study is in reasonable agreement with/only slightly higher than, for example, the 0.9% to 1.3% annual rates of GI-related hospitalizations due to NSAID use derived from certain epidemiological studies.[3,10]

The XX% annualized incidence of NSAID-related ulcer complications is also consistent with incidences obtained from studies using similar pre-specified criteria. For instance, a 1.9% annual incidence of upper GI ulcer complications due to NSAID use was found in the MUCOSA study.[4] Similarly, other studies that examined the effect of selective COX-2 inhibition on the development of upper GI ulcer complications reported an annualized incidence of 1.68% to 1.8%.[16,11] Based on these comparisons, it appears that our method of reviewing and adjudicating upper GI ulcer complications was sensitive and reliable.

While gastroduodenal ulcers detected by upper GI endoscopy have been considered by some as surrogate markers for upper GI ulcer complications, their reliability as antecedents to NSAID-induced upper GI ulcer complications has been questioned, given that endoscopic ulcers can be identified in over 20% of NSAID users and that significant upper GI ulcer complications may occur without prior evidence of mucosal damage.[12,13,14,15,16] Interestingly, we observed that the relative reductions in the rates of gastroduodenal ulcers confirmed by endoscopy or x-ray (XX%) and upper GI ulcer complications (XX%) in celecoxib-treated patients were in reasonably good agreement. Another indicator that has been used for upper GI ulcer complications is a composite end point consisting of upper GI perforation, ulceration, and bleeding (PUB).[18] In this regard, it has been suggested that this approach is also limited, since it combines commonly occurring ulcers with much less frequently occurring perforations and bleeding.[17] Rather, a composite end point comprised of upper GI perforation, obstruction, and bleeding, such as the one used in the present analysis, may be a more accurate indicator of clinically significant upper GI ulcer complications.

We also chose to compare celecoxib against more than one NSAID, since it had been previously reported that individual NSAIDs can produce varying degrees of upper GI toxicity.[18] Ibuprofen and diclofenac were selected as comparators because these NSAIDs are generally associated with the lowest frequencies of upper GI ulcer complications.[19] Since our data show that celecoxib has a lower potential than either ibuprofen or diclofenac for producing upper GI ulcer complications, it is reasonable to conclude that celecoxib is most likely superior to all NSAIDs in terms of upper GI safety.

Given the patient population selected for the study and the necessity for a chronic treatment period, it was not possible to include a placebo arm in the trial. However, historical data indicate that the annualized incidence of upper GI ulcer complications for celecoxib reported here is comparable to previously published incidences, which ranged from 0% to 0.9%, for patients of reasonably similar demography and medical history who were not taking NSAIDs.[3,16,17,18] Therefore, it is plausible that the risk of upper GI ulcer complications associated with long-term use of celecoxib may be similar to the background incidence in non-treated patients.

Advanced age has been identified as one of the primary risk factors for NSAID-induced ulcer complications. Many studies have also identified one or more of the following risk factors: higher doses, history of upper GI injury (e.g., gastroduodenal ulceration and upper GI bleeding), concomitant corticosteroid use, concomitant anticoagulant use, and a history of cardiovascular disease.[20,21] (1) Our results confirm previous findings. Patients over the age of 65/with a history of XX/who were concurrently taking XX had a XX-fold greater risk of

experiencing an upper GI ulcer complication. (2) The precise cause(s) the ulcer complications that developed in patients treated with celecoxib in our study are not readily apparent. Age, disease type and duration, history of GI disease, history of cardiovascular disease, *H. pylori* status, concurrent medication use, alcohol use, and tobacco use did not appear to predispose to upper GI ulcer complications in our study.

NSAID-related GI toxicity ranges in severity from life-threatening ulcer complications to asymptomatic ulcers or side effects, such as abdominal pain, dyspepsia, and nausea. Our data indicate that the occurrence of GI-related adverse events was lower in the celecoxib group (XX%) than in either the ibuprofen (XX%) or diclofenac (XX%) group; the incidence of other untoward effects, such as renal and hepatic effects, was not significant. Notably, this rate is similar to the withdrawal rates associated with celecoxib use in studies of substantially shorter duration.[14,15,22] It appears then that celecoxib is generally well tolerated even with long-term use. Considering that it has been estimated that approximately 20% to 30% of patients receiving NSAIDs develop peristent GI-related adverse events and that as many as 10% discontinue treatment because of these symptoms,[3,23] our findings may have important implications on improving treatment compliance in OA and RA patients.

In the present study, celecoxib relieved the pain and inflammation due to OA and RA as effectively as both ibuprofen and diclofenac. The reduction in pain was meaningful to patients in all treatment groups as assessed by the SF-36 Health Survey and the HAQ. These findings, in conjunction with the above results, indicate that celecoxib provides sustained arthritis efficacy without detrimental effects on GI safety and tolerability.

Based on our findings, we conclude that long-term use of celecoxib is associated with a significantly lower risk of clinically significant upper GI ulcer complications than long-term use of either ibuprofen or diclofenac. Overall, our analysis indicates that celecoxib can reduce the risk of mild to life-threatening NSAID-mediated upper GI tract injury when used chronically for the treatment of OA or RA.

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Table 1. Definitions and Adjudication Criteria for Ulcer Complications

Event	Criteria for Confirmed Event
Gastric or duodenal perforation	A perforated lesion that required surgery. It could involve a laparoscopic repair, but only if evidence of the perforation was unequivocal, such as free air in the abdomen visible by x-ray, or peritoneal signs upon physical examination.
Gastric outlet obstruction	Gastric outlet obstruction was required to be diagnosed by the investigator, and the diagnosis was required to be supported by endoscopy (e.g., ulcer with a tight edematous pyloric channel) or by x-ray results (e.g., a dilated stomach, delayed barium emptying with clinical evidence of outlet obstruction and with an ulcer in the channel, or severe outlet narrowing and edema)

Upper GI bleeding	• hematemesis with a lesion (ulcer or large erosion) at endoscopy or x-ray
	• lesion (ulcer or large erosion) at endoscopy with evidence of active bleeding or stigmata of a recent hemorrhage (visible vessel or clot attached to the base of an ulcer)
	• melena with a lesion (ulcer or large erosion) at endoscopy or x-ray with evidence of serious bleeding, which included at least one of the following:
	  • decrease in hematocrit (of at least 5 percentage points) or decrease in hemoglobin (greater than 1.5 g/dL relative to baseline)
	  • signs of postural vital sign changes (increase in pulse rate of at least 20 bpm and/or decrease in systolic blood pressure of at least 20 mm Hg and/or in diastolic blood pressure of at least 10 mm Hg)
	  • transfusion of more than two units of blood
	  • blood in the stomach at endoscopy or nasogastric aspiration

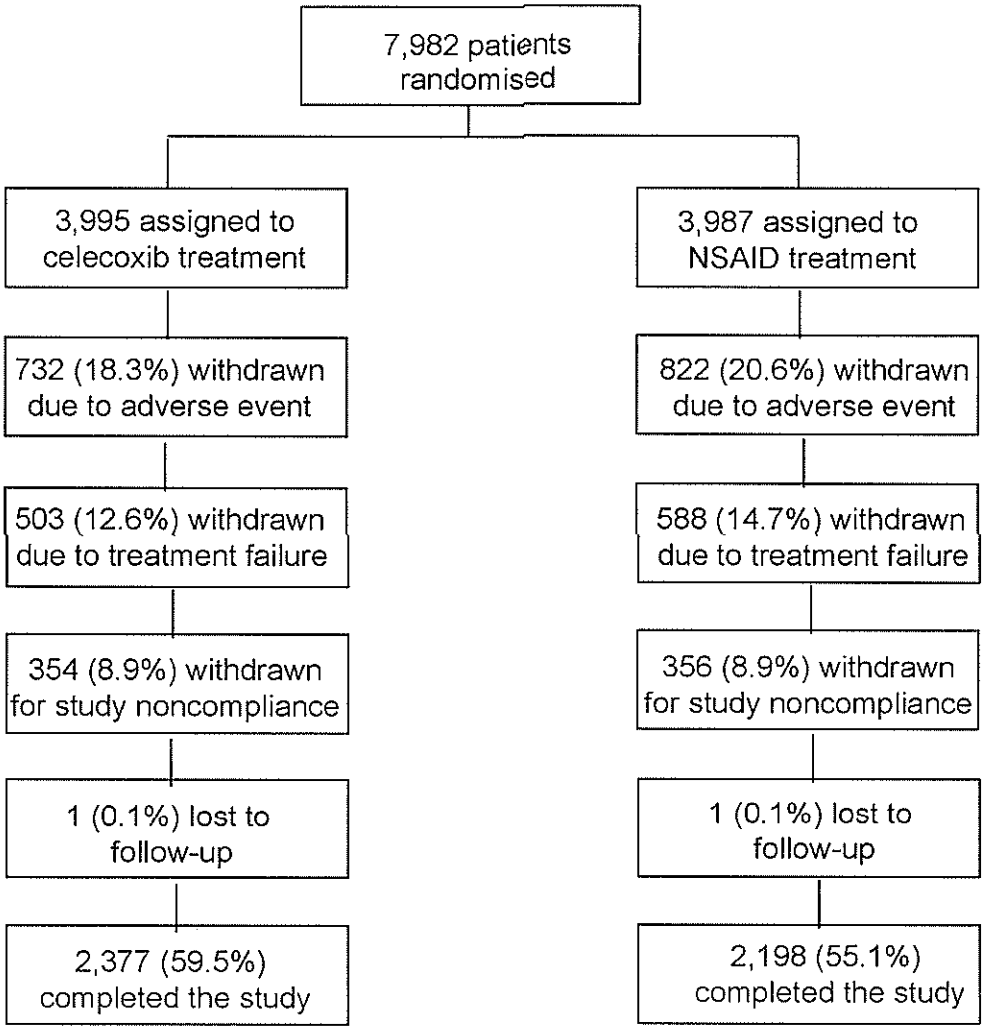

7,982 patients randomised
3,995 assigned to celecoxib treatment
3,987 assigned to NSAID treatment
732 (18.3%) withdrawn due to adverse event
822 (20.6%) withdrawn due to adverse event
503 (12.6%) withdrawn due to treatment failure
588 (14.7%) withdrawn due to treatment failure
354 (8.9%) withdrawn for study noncompliance
356 (8.9%) withdrawn for study noncompliance
1 (0.1%) lost to follow-up
1 (0.1%) lost to follow-up
2,377 (59.5%) completed the study
2,198 (55.1%) completed the study

Table 1. Baseline Characteristics and Patient Demographics

Characteristic	Celecoxib 400 mg BID (n = 3995)	NSAIDs (n = 3987)
Mean age (range), y	60.6 (20-89)	59.8 (18-90)
>65 years of age (%)	36.5	34.2
>75 years of age (%)	10.4	9.2
Women, (%)	68.5	69.1
Race, (%)		
White	88.5	87.8
Black	7.5	8.1
Hispanic	2.7	2.8
Asian	0.8	0.7
Other	0.5	0.6
Primary disease, (%)		
RA	27.3	27.5
Mean (SD) duration of disease, y		
OA	10.2 (9.7)	10.1 (9.9)
RA	11.3 (9.9)	10.7 (9.6)
Potential Risk Factor (%)		
History of GI bleeding	1.7	1.5
History of GI ulcer	8.4	8.1
Positive *Helicobacter pylori* infection (%)	37.1	36.7
Tobacco use, (%)	15.8	14.9
Alcohol use, (%)	30.9	30.1
Concurrent medications, (%)		
Aspirin (≤325 mg daily)	21.8	21.3
Corticosteroids	30.2	29.3
DMARDs	?	?
Anticoagulants	0.5	0.9

Table 2. Incidence of Potential Clinically Significant upper GI Ulcer Complications

Category	Celecoxib 400 mg BID (n = 3,995)	NSAIDs (n = 3,987)
Total potential cases reported	677	837* (need 6 mo)
Total cases adjudicated	162	211*
Not meeting the definition of an ulcer or POB	82	96
Esophageal Disease		
esophagitis	11	11
esophageal ulcer	1	2
esophageal stricture	1	1
Mallory-Weiss tear	2	-
esophageal carcinoma	1	-
Gastroduodenitis		
gastritis	13	18
duodenitis	3	1
Colonic or Small Bowel Disease		
diverticular disease		
colitis/proctitis	-	2
colon polyps/carcinoma	1	2
small bowel obstruction	1	1
	-	1
Non-ulcer bleeding		
diverticular		
hematochezia	7	1
hemoccult positive stool	3	10
AVMS	7	6
unknown	-	1
	-	1
Miscellaneous GI symptoms		
abdominal pain		
dyspepsia	8	7
GERD	10	9
nausea/vomiting	6	6
chest pain	-	1
	-	1
Miscellaneous		
anemia	5	12
hemorrhoids	1	2
cholethiasis	1	-
Total definite ulcer complications		

Table 2. Number of Potential Cases Reported, Adjudicated Cases, Gastroduodenal Ulcers, and Ulcer Complications that Met Pre-specified Definitions

Category	Celecoxib 400 mg BID (n = 3,995)	NSAIDs (n = 3,987)
Total potential cases reported	677	837* (need 6 mo)
Total cases adjudicated	112	145*
Esophageal disease	16	14
Gastroduodenitis	16	19
Colonic or small bowel disease	2	6
Non-ulcer bleeding	18	21
Miscellaneous GI symptoms	24	24
Anemia	5	12
Cholelithiasis	1	-
Total cases not meeting the definition of a gastrodoudenal ulcer or ulcer complication	82	96
Gastroduodenal ulcers and ulcer complications	30	49
Ulcer complications only	11	20

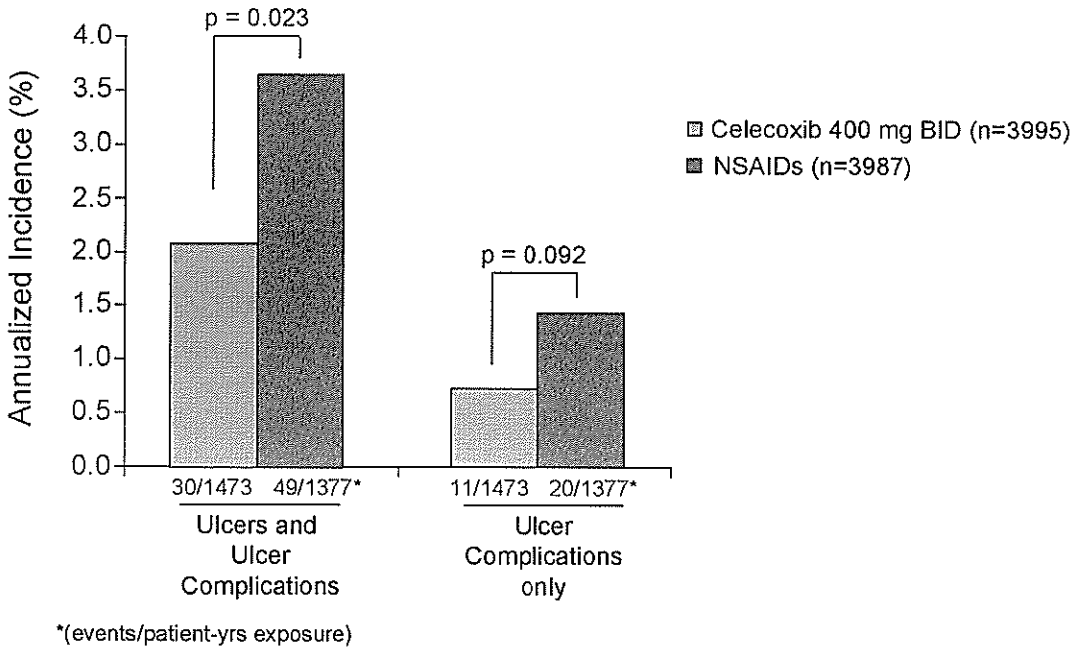
Table 3. Adverse Events

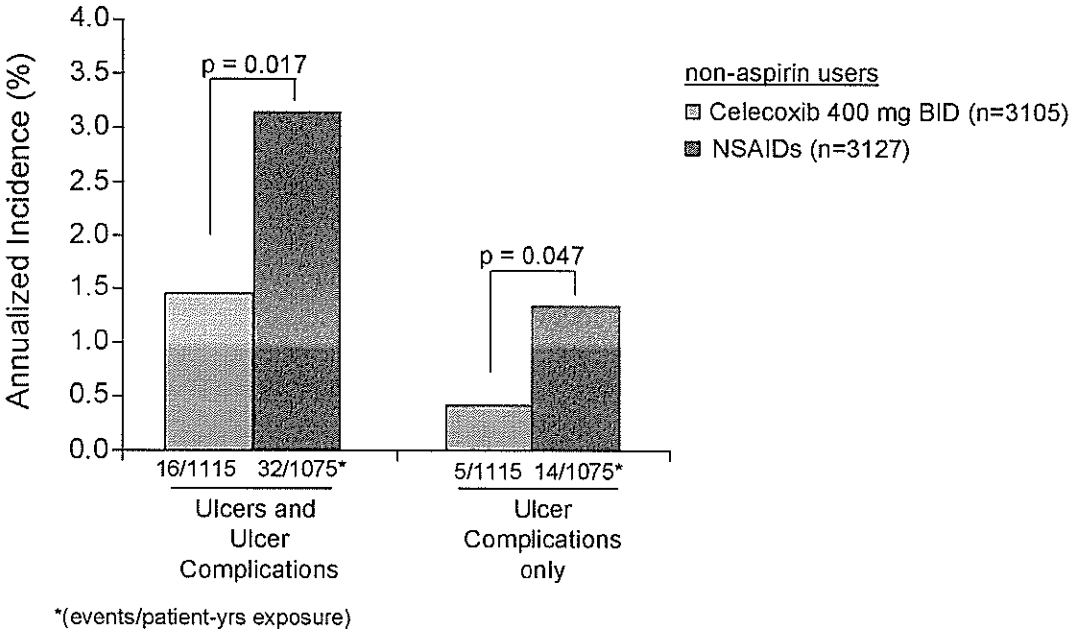
Characteristic	Celecoxib 400 mg BID (n = 3995)	NSAIDs (n = 3987)
GI Adverse Effects		
Dyspepsia	16.5	18.0
Abdominal pain	11.7	14.9*
Diarrhea	10.9	11.2
Nausea	8.2	10.5*
Constipation	2.2	6.7*
Withdrawals		
Hepatic Adverse Effects		
Increased SGPT	1.0	3.1*
Increased SGOT	0.9	2.6*
Abnormal hepatic function	0.3	1.0*
Withdrawals		
Bleeding-Related Adverse Effects		
Anemia	4.5	7.0*
Ecchymosis	1.1	1.3
Withdrawals		
Renal Adverse Effects		
Peripheral edema	3.7	4.4
Increased creatinine	1.3	1.5
Withdrawals		

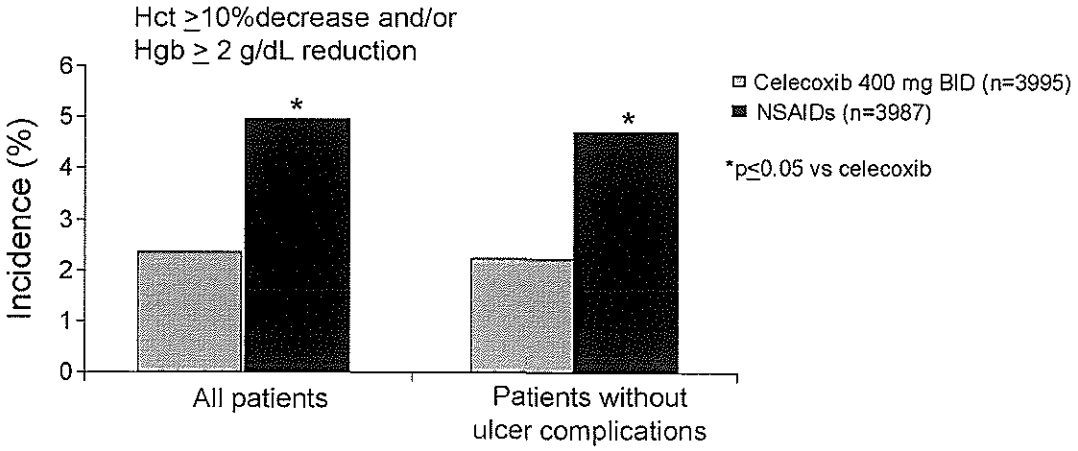
Non-Resp.

Non-Resp.

Non-Resp.


p = 0.023
p = 0.092
Annualized Incidence (%)
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Celecoxib 400 mg BID (n=3995)
NSAIDs (n=3987)
30/1473 49/1377*
11/1473 20/1377*
Ulcers and Ulcer Complications
Ulcer Complications only
*(events/patient-yrs exposure)


p = 0.017
p = 0.047
Annualized Incidence (%)
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
non-aspirin users
Celecoxib 400 mg BID (n=3105)
NSAIDs (n=3127)
16/1115 32/1075*
5/1115 14/1075*
Ulcers and Ulcer Complications
Ulcer Complications only
*(events/patient-yrs exposure)


Hct ≥10%decrease and/or
Hgb ≥ 2 g/dL reduction
Incidence (%)
0
1
2
3
4
5
6
*
*
All patients
Patients without ulcer complications
Celecoxib 400 mg BID (n=3995)
NSAIDs (n=3987)
*p≤0.05 vs celecoxib

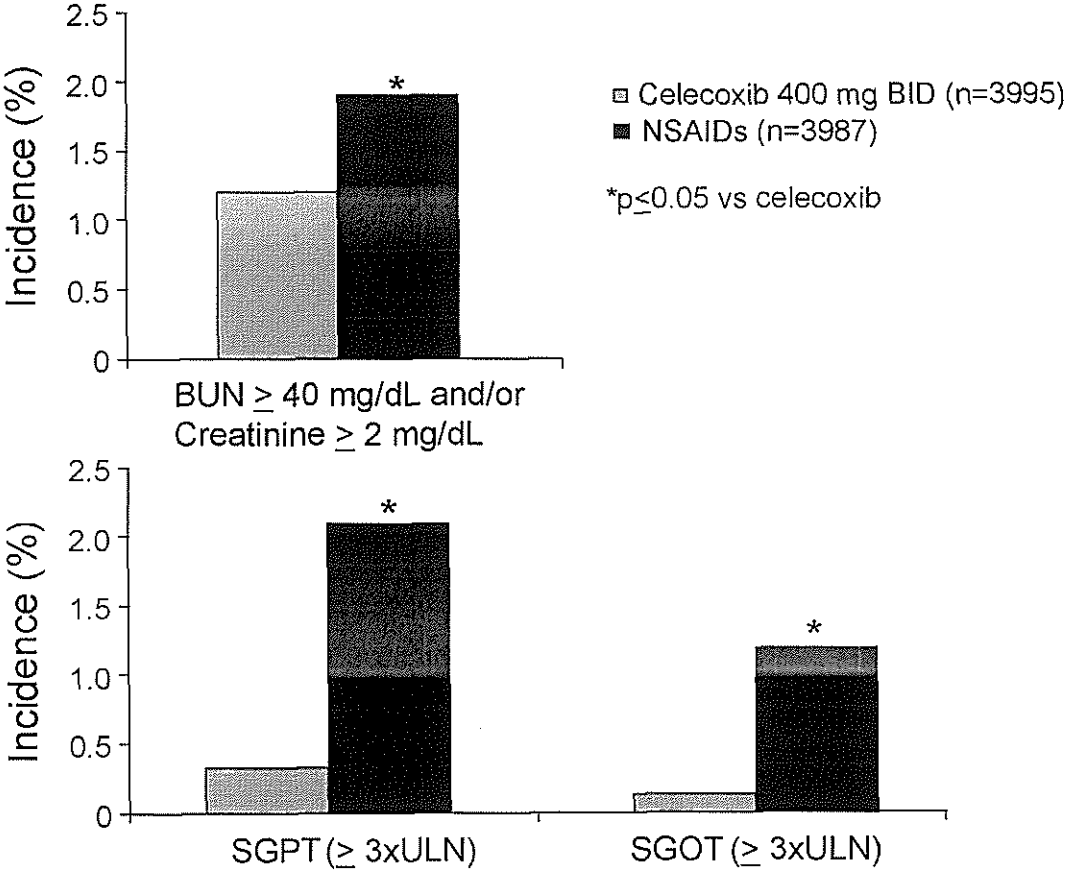

Incidence (%)
2.5
2.0
1.5
1.0
0.5
0
*
BUN ≥ 40 mg/dL and/or
Creatinine ≥ 2 mg/dL
Celecoxib 400 mg BID (n=3995)
NSAIDs (n=3987)
*p≤0.05 vs celecoxib
Incidence (%)
2.5
2.0
1.5
1.0
0.5
0
*
*
SGPT (≥ 3xULN)
SGOT (≥ 3xULN)

Table 6. Representative Clinical Laboratory Measurements

Measurement	Celecoxib 400 mg BID (n = XX)	Ibuprofen 800 mg TID (n = XX)	Diclofenac 75 mg BID (n = XX)
Blood pessure, mm Hg Systolic Baseline Final vsit Diastolic Baseline Final vsit			
Hemoglobin, g/L Baseline Final visit			
Creatine, µmol/L Baseline Final visit			
Alanine aminotransferase, U/L Baseline Final visit			
Aspartate aminotransferase, U/L Baseline Final visit			

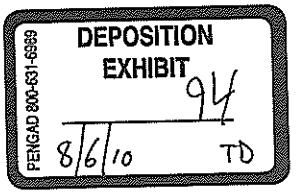
BEGNO	ENDNO	BEGATTACH	ENDATTACH	PGS	DOCDATE	AUTHORNAM	CUSTODIAN
DEFS 01628309	DEFS 01628341			33	04/15/2000	Searle	Verburg, Kenneth

EXHIBIT 150

From: LEFKOWITH, JAMES B. [PHR/1825]
Sent: Thursday, May 25, 2000 7:27 PM
To: ISAKSON, PETER C [PHR/1005]; FRIEDMAN, MICHAEL A [PHR/1825]; NEEDLEMAN, PHILIP [UNK/1000]; JORDAN, DAVID C. [PHR/1825]; ZHAO, WILLIAM W [PHR/1825]; BURR, AIMEE M. [PHR/1825]; KENT, JEFFREY D [PHR/1825]; VERBURG, KENNETH M [PHR/1825]; GEIS, GEORGE S. [PHR/1825]
Subject: CBX-0375154_CLASS ms

CBX-0375155_CLAS S_manuscript.v...

For your reading pleasure.
JL



THE CELECOXIB LONG-TERM ARTHRITIS SAFETY STUDY (CLASS)

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Running Title: Upper GI Safety of Celecoxib

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ABSTRACT

Context: Use of nonsteroidal anti-inflammatory drugs (NSAIDs) is associated with upper gastrointestinal (GI) toxicity caused by inhibition of GI mucosal cyclooxygenase (COX)-1. Celecoxib specifically inhibits COX-2 and has demonstrated a low potential for producing GI injury.

Objective: To compare the incidence of significant upper GI toxicity in patients with rheumatoid arthritis (RA) or osteoarthritis (OA) treated with 2- to 4-times the maximum therapeutic doses of celecoxib, respectively, versus two NSAID comparators administered at standard therapeutic doses.

Design: Randomized, multicenter, double-blind trial from October 1998 through January 2000. All patients were provided the opportunity to complete at least six months of treatment.

Setting: Three hundred eighty clinical sites in the United States and Canada.

Patients: A total of 7,968 patients aged 18 years and older with OA (n= 5,746) or RA (n= 2,183) who met inclusion criteria were randomized; 4,575 (57%) patients completed 6 months of treatment or withdrew prior to 6 months..

Interventions: Patients were randomized to receive celecoxib 400 mg twice daily (n=3,987), ibuprofen 800 mg three times daily (n=1,996) or diclofenac 75 mg twice daily (n=1,985) in 2:1:1 proportions. Concomitant low dose aspirin use (≤325 mg daily) for cardiovascular prophylaxis was permitted.

Main Outcome Measures: Incidence of upper GI ulcer complications (bleeding, perforation and obstruction) and symptomatic ulcers, or ulcer complications alone, for celecoxib versus NSAIDs that met pre-specified criteria judged by a blinded expert adjudication committee.

Results: For the entire cohort, the annualized incidence rates of upper GI ulcer complications alone, or combined with symptomatic ulcers, for celecoxib vs. NSAID comparators were 0.76% vs. 1.45% (p=0.092; relative risk = 0.53; 95% confidence interval (CI) 0.26 to 1.11) and 2.08% vs 3.54% (p=0.023; relative risk = 0.59; 95% CI 0.38 to 0.94). Removing the confounding effect of concomitant aspirin use, the annualized incidence rates of upper GI ulcer complications alone, or combined with symptomatic ulcers, for celecoxib vs. NSAID comparators were 0.44% vs.1.27% (p=0.037; relative risk = 0.35; 95% CI 0.14 to 0.98) and 1.40% vs 2.91% (p=0.017; relative risk = 0.48; 95% CI 0.28 to 0.89). Overall, celecoxib was better tolerated than NSAID comparators as fewer celecoxib-treated patients experienced GI, hepatic, renal or hemostasis-related adverse effects. [redacted] Non-Resp.

[redacted] Non-Resp.

Conclusion: Celecoxib, at 2- to 4-times the maximally effective RA and OA doses, was associated with a lower incidence of significant upper GI toxicity and other adverse effects than NSAID comparators at standard therapeutic doses. This study validates celecoxib's unique mechanism of action and intrinsic general safety profile.

Key words: ulcer complications, symptomatic ulcers, cyclooxygenase, NSAIDs, celecoxib

Word Count: 3730 (manuscript), 431 (abstract)

INTRODUCTION

Musculoskeletal disorders are extremely common and represent a frequent cause of health care resource utilization.[1] For such disorders, nonsteroidal anti-inflammatory drugs (NSAIDs) are a mainstay of clinical care and are the preferred agent by patients.[2-4] Well-established limitations of NSAID therapy include the risk of developing significant injury to the upper gastrointestinal (GI) tract, primarily ulceration or complications resulting from an ulcer such as perforation, gastric outlet obstruction and hemorrhage. Based on epidemiological and controlled trial experience, there is an estimated two- to ten-fold greater risk for upper GI injury in NSAID users when compared to nonusers.[5-11] The annualized incidence rate of upper GI ulcer complications and symptomatic ulcers in NSAID users ranges from 2 to 4% and 1 to 2% for ulcer complications alone.[12-16]

It is known that NSAIDs inhibit cyclooxygenase (COX), the enzyme responsible for the conversion of arachidonic acid to prostaglandins.[17] The ulcerogenic effects of these agents are attributed to interference with prostaglandin formation, thereby, leading to inadequate mucosal protection in the upper GI tract.[18;19] COX exists in two isoforms.[20-23] COX-1 is a ubiquitous constitutive isozyme; both gastrointestinal prostaglandins and platelet-derived thromboxane A_2 are formed exclusively from COX-1. Alternatively, COX-2 is largely a cytokine-induced isozyme producing prostaglandins that mediate pain and inflammation.[24-30] NSAIDs inhibit both COX-1 and COX-2 to varying degrees.[31;32] Thus, the therapeutic effects of NSAIDs are derived from inhibition of COX-2, while the adverse effects of these agents within the upper GI tract or with respect to platelet function arise from inhibition of COX-1 activity.

Celecoxib (Celebrex) is a recently approved agent for treating the inflammation and pain of arthritis that specifically inhibits COX-2. Celecoxib appears to have little potential to produce upper GI injury as evidenced by a four-fold to six-fold lower association with gastroduodenal ulceration than either naproxen or diclofenac in endoscopic studies.[33;34] In these same trials, the risk of gastroduodenal ulceration in celecoxib-treated patients was comparable to placebo. A pooled analysis of 14 randomized controlled trials of arthritis patients also indicated that the incidence of upper GI ulcer complications associated with celecoxib was eight-fold lower than that found with diclofenac, ibuprofen and naproxen combined.[16]

In order to establish the distinct nature of the underlying biochemical mechanism of celecoxib more rigorously, however, it was essential to perform a prospective, randomized, double-blind study to determine the incidence of upper GI ulcer complications alone or combined with symptomatic gastroduodenal ulcers among arthritis patients chronically receiving celecoxib or NSAIDs. To clearly establish that celecoxib is COX-1 sparing, our study compared celecoxib administered at 2- to 4-times the maximum effective doses for RA and OA, respectively, to common therapeutic doses of ibuprofen and diclofenac, two non-specific NSAIDs commonly used to treat OA and RA. Concomitantly, this study served to assess more broadly the safety of celecoxib at supratherapeutic doses with respect to other potentially mechanism-based, as well as idiosyncratic, toxicities.

METHODS

Study Population

Men and women outpatients 18 years of age and older were eligible to participate in the study they were diagnosed with OA or RA evident for 3 months or longer and were expected to require continuous treatment with an NSAID for the duration of the trial. Patients were excluded from the study participation if they had active GI, renal, hepatic, or coagulation disorders; malignancy (unless removed surgically with no recurrence within 5 years); esophageal or gastroduodenal ulceration within the previous 30 days; a history of gastric or duodenal surgery other than an oversew; or known hypersensitivity to COX-2 inhibitors, sulfonamides, ibuprofen, or diclofenac. Women were excluded if they were pregnant, might become pregnant, or were lactating.

Study Protocol

This prospective, randomized, double-blind trial was conducted at 380 centers in the United States and Canada from December 1998 to January 2000 in accordance with the principles of good clinical practice and the Declaration of Helsinki. The protocol was approved by the institutional review board at each study site and all patients were required to provide written informed consent.

Prior to enrollment, patients completed a physical examination and clinical laboratory testing, including a baseline serological test for *Helicobacter pylori* antibodies (FlexSure, Beckman-Coulter, Palo Alto, CA). After a baseline visit, follow-up clinic visits took place at weeks 4, 13, 26, and every 13 weeks thereafter (if necessary) after the initial dose of medication.

Monitoring for adverse events and clinical laboratory testing were repeated at all follow-up visits. All patients were given the opportunity to complete a minimum of 6 months of treatment.

Treatment

Patients were randomly assigned by a computer-generated randomization schedule to receive either celecoxib 400 mg BID or the comparator NSAID (ibuprofen 800 mg TID or diclofenac 75 mg BID) on a 2:1:1 basis. All treatment regimens were fully masked to ensure they were identical in appearance and that patients took the same number of capsules.

Concomitant Medications

NSAIDs (except for stables doses of aspirin up to 325 mg daily); anti-ulcer drugs (except for single dose antacid use daily or multiple dose use up to 7 days each month); antibiotics used alone or in combination with omeprazole, lansoprazole, and ranitidine for treatment of *H. pylori* infection; and antineoplastics were prohibited during the course of the study. Use of oral, intramuscular, and intra-articular corticosteroids, and DMARDs were permitted.

Clinical Assessments

Investigators were instructed to identify and report all potential upper GI ulcer complications. Evaluation of such events was outlined in a pre-specified algorithm structured to reproduce clinical practice norms. Evaluation was required for any of the following presentations: severe acute abdominal pain or acute abdomen; intractable abdominal pain with nausea or vomiting; hematemesis or melena; acute hypovolemia [redacted] Non-Resp. history of melena within the past

14 days or black stool representing a change in normal pattern; development of postural dizziness or lightheadedness, or syncope; history of vaguely characterized dark stool, or dark stool within the past 14 days or with concurrent iron or bismuth ingestion; history of hematochezia, or anal or rectal bleeding after elimination; development of new anemia or decrease in hematocrit of 5% of more; development of dyspepsia, abdominal pain, or nausea or vomiting; or development of heme-positive stools. Endoscopy was encouraged to document bleeding lesions but could also be performed if indicated by the investigator's clinical judgement.

All documentation relating to potential ulcer complications was forwarded to a Gastrointestinal Events Committee (comprised of Jay Goldstein, MD, Naurang Agrawal, MD, Glenn Eisen, MD, and William Stenson, MD). The Committee was established to review and adjudicate all potential events according to prospectively established upper GI ulcer complication definitions as provided in Table 1. The Committee collectively reviewed each case in a blinded fashion and assigned it by consensus as either meeting or not meeting the definition of an upper GI ulcer complication. Symptomatic ulcers comprised those cases that did not meet the definition of an ulcer complication, but did have endoscopic or x-ray evidence of a gastric or duodenal ulcer as judged by the Committee. All patients with symptomatic ulcers or ulcer complications were withdrawn from the study.

Statistical Analysis

The sample size calculations were based on the assumption that the annualized incidence of upper GI ulcer complications would be 0.3% for celecoxib and 1.2% for NSAIDs. To detect

this difference with a 5% significance level (two-sided) and a power of 85% and assuming a 30% withdrawal rate, a sample size of 4,000 patients was required for the celecoxib group and 2,000 patients for each NSAID group.

Homogeneity of the treatment groups at baseline was analyzed by using the chi-square test for categorical variables and two-way ANOVA with treatment and center effects for continuous variables. All statistical analyses were conducted on the intent-to-treat populations that consisted of all patients who received at least one dose of assigned study medication. Time-to-event analyses of upper GI ulcer complications alone or combined with symptomatic ulcers were performed based on Kaplan-Meier estimates of cumulative event rates, but are expressed in the text as annualized incidence rates. Log-rank tests were used to compare the incidence rates based on the Kaplan-Meier estimate. The effect of potential risk factors for the development of an ulcer complication (including but not limited to concurrent aspirin use) were pre-specified and analyzed by Cox proportional hazards model. Treatment-related differences in the incidence of adverse effects or clinical laboratory changes were determined by Fisher's exact test.

RESULTS

A total of 7,968 patients were enrolled. Of these, 3,987 patients were treated with celecoxib 400 mg BID and 3,981 patients were treated with NSAIDs (1,996 received ibuprofen 800 mg TID and 1,985 received diclofenac 75 mg BID). Total patient-years of exposure were 1,473 and 1,377 in the celecoxib and NSAID treatment groups, respectively. There were no clinically meaningful differences in baseline characteristics between groups (Table 2). Mean age overall was 60 years (range 18-90 years); 38% of the patients were 65 years or older, 69% were women and 73% were diagnosed with OA. Approximately, 10% of the patients in each group had a prior medical history of a peptic ulcer or upper GI bleeding and over 20% of the patients were taking low dose aspirin (≤325 mg daily) for cardiovascular prophylaxis. Approximately 57% of the patients (n=4,573) completed six months of treatment. Figure 1 shows reasons for early discontinuation from the study. More patients in the NSAID treatment group withdrew from the study for either adverse effects or for lack of efficacy than did celecoxib-treated patients ($p<0.05$). No patients were lost to follow-up.

The crude rate of potential upper GI ulcer complications reported by investigators to the Events Committee over 6 months was significantly lower in celecoxib-treated patients than with NSAIDs (16.0% vs 12.6%, $p<0.001$). All reports were reviewed by the Events Committee and a total of 261 cases of potential upper GI ulcer complications were selected for adjudication (the remainder being cases of either isolated GI symptoms or anemia without further evidence of a potential event). Upon adjudication, the Events Committee identified 35 upper GI ulcer complications and another 48 cases that represented symptomatic, but uncomplicated, gastroduodenal ulcers (Table 3). All but one of the upper GI ulcer complications (a gastric

outlet obstruction in a celecoxib-treated patient) represented bleeding events in which an ulcer or large erosion was associated with either visual evidence of bleeding, melena, or occult blood-positive stools and a decrease in hematocrit or hemoglobin. Four upper GI ulcer complications (2 in celecoxib patients and 2 in NSAID-treated patients) were censored from the analysis owing to the timing of the event as prespecified by the Events Committee (within 48 hours after the first dose day or after 14 days after the last known dose). The remaining 178 cases were judged by the Committee to represent neither an upper GI ulcer complication nor a symptomatic ulcer and were assigned a diagnosis under the categories listed in Table 3.

The annualized incidence of upper GI ulcer complications in celecoxib-treated patients based on 6 months exposure was approximately one-half the rate observed in patients taking NSAIDs (0.76% vs 1.45%, p=0.092, Figure 2 top panel). The relative risk over 6 months for celecoxib compared to NSAIDs was 0.53 (95% CI, 0.26-1.11). The annualized incidence of upper GI ulcer complications plus symptomatic ulcers with celecoxib was significantly lower than with NSAIDs (2.08% vs 3.54%, p=0.023, Figure 2 top panel). The relative risk over 6 months for celecoxib compared to NSAIDs was 0.59 (95% CI, 0.38-0.94).

Based on survival analyses with a Cox proportional hazard model, low dose aspirin use was found to have a statistically significant effect (p=0.005) on the incidence of upper GI ulcer complications (alone or in combination with symptomatic ulcers) in the celecoxib-treated patients. Within the celecoxib treatment group, an upper GI ulcer complication was nearly 4-fold more common in aspirin users occurring in 6 of 833 patients (0.7%) taking low dose aspirin vs 5 such events in 3,154 (0.2%) non-aspirin users. Low dose aspirin use did not have a

significant effect on the rate of upper GI ulcer complications in patients receiving NSAIDs (p=0.21). In consequence, the non-aspirin using cohort was examined independently.

The annualized incidence of upper GI ulcer complications over 6 months in non-aspirin users was significantly lower with celecoxib vs NSAIDs (0.44% vs 1.27%, p=0.037, Figure 2 bottom panel). The relative risk over 6 months for celecoxib compared to NSAIDs was 0.35 (95% CI, 0.14-0.98). The annualized incidence of upper GI ulcer complications plus symptomatic ulcers over 6 months in patients not taking aspirin users was also significantly lower with celecoxib than with NSAIDs (1.40% vs 2.91%, p=0.017, Figure 2 bottom panel). The relative risk over 6 months for celecoxib compared to NSAIDs was 0.48 (95% CI, 0.28-0.89).

Celecoxib, administered at 2- to 4-times the maximum effective RA and OA doses respectively, was safe and generally well-tolerated when chronically administered as compared to standard therapeutic doses of either ibuprofen or diclofenac. The adverse effects with the highest incidence in either treatment group were dyspepsia, upper respiratory infection, headache, abdominal pain and diarrhea.

Celecoxib was associated with better GI tolerability than NSAID treatment. The overall incidence of GI adverse effects experienced by patients taking celecoxib was significantly lower than with NSAIDs (40% vs 45%; p<0.001) as was the rate of withdrawal due to GI intolerability (Table 4). Of the most commonly reported GI adverse effects, dyspepsia, abdominal pain, nausea, and constipation were significantly less common (p<0.001) with

celecoxib than with NSAIDs (Table 4). Similar effects were seen in the cohort of patients not taking low dose aspirin.

Significantly less hemostasis-related adverse effects (anemia, ecchymoses, hematochezia) and withdrawals due to such were observed in patients receiving celecoxib when compared to NSAID-treated patients (Table 4). Celecoxib was also associated with a lower incidence ($p<0.05$) of clinically meaningful reductions in hematocrit or hemoglobin for the entire patient cohort (Figure 3). This difference persisted when all patients with potential upper GI events were excluded from the analysis, thus removing all patients with ulcer complications, symptomatic ulcers or other diagnosed GI pathology (Figure 3). In parallel with changes seen in hematocrit and hemoglobin, serum iron to iron binding capacity ratios tended to increase on celecoxib and decrease on NSAIDs (+1.4% vs -2.4%, $p<0.05$).

As shown in Figure 4, the incidence of serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevations that exceeded 3 times the upper limit of normal was 5- to 10-fold higher ($p<0.05$) in patients receiving NSAIDs than with celecoxib. Similarly, investigators reported a significantly higher ($p<0.05$) incidence of elevated serum transaminases with NSAID treatment (Table 4). Study withdrawals due to elevated serum transaminases were also higher in patients receiving NSAIDs. Most liver function enzyme elevations occurred in patients receiving diclofenac.

The incidence rates of renal-related adverse effects such as peripheral edema, [redacted] Non-Resp. [redacted] Non-Resp. [redacted], were similar between the treatment groups (Table 4). However, an

elevated serum creatinine was noted more frequently by investigators in patients on NSAIDs than in patients on celecoxib ($p<0.05$). Also, a greater number of patients ($p<0.05$) receiving NSAIDs were found with elevations in serum creatinine levels above 2 mg/dL and/or BUN values above 40 mg /dL than with celecoxib (Figure 4). Celecoxib was associated with a significantly higher incidence ($p<0.05$) of rash and pruritus and study withdrawals due to cutaneous adverse effects as compared to NSAID therapy (Table 4). [redacted] Non-Resp.

[redacted] Non-Resp.

Serious adverse effects (representing hospitalizations or malignancies detected during study participation) were reported for 4.3% of patients receiving celecoxib and 4.2% of NSAID patients. The most common serious adverse effects were accidental fractures, pneumonia, [redacted] Non-Resp. consistent with expected co-morbidities in this patient population. No serious rashes or unexpected serious adverse events were observed in patients on celecoxib. No treatment-related differences were observed.

DISCUSSION

Our study establishes that celecoxib when used chronically at 2- to 4-times the maximum effective doses for RA and OA, respectively, is associated with a lower incidence of upper GI ulcer complications and symptomatic ulcers than comparator NSAIDs (ibuprofen and diclofenac) at standard therapeutic doses. This study thus directly addresses the critical safety issue inherent to COX-2 specificity, namely that COX-2 specific inhibitors are associated with a reduction in upper GI toxicity relative to non-specific COX inhibitors. In addition, the data presented herein support the overall safety and tolerability of celecoxib, part of which may be mechanism-dependent and part of which may be specific to the pharmacology of this agent. It is worth noting that a clinical trial using an NSAID at supratherapeutic doses (similar to those used for celecoxib in the current trial) would not be feasible given the known toxicology of NSAIDs.[35-38]

The driving force behind the development of COX-2 specific inhibitors has been a widening appreciation of the mechanism-based GI toxicity of NSAIDs. The public health impact of NSAID-related upper GI toxicity is substantial. Based on the NSAID-attributable incidence of ulcer complications, it has been estimated that such complications lead to approximately 107,000 hospitalizations and 16,500 deaths yearly in the US.[11]

In this study, the incidence of an upper GI ulcer complication combined with symptomatic ulcers associated with NSAID comparators was 3.54%, with an incidence of ulcer complication alone of 1.45%. In comparison, the corresponding rates associated with supratherapeutic doses of celecoxib in this study were 2.08% and 0.76%, respectively, the difference in

symptomatic ulcers and ulcer complications being statistically significant. The lack of a statistical significant separation of upper GI complications associated with celecoxib when compared to NSAIDs in the entire study cohort was largely a function of the higher than expected event rate observed in the celecoxib treatment group relative to the previously reported annualized incidence rate of 0.2% obtained from a pooled analyses of 14 randomized controlled trials ranging from 2 to 24 weeks in duration.[16]

This increase was attributable to concurrent low-dose aspirin use. The percentage of patients using low-dose aspirin for cardiovascular prophylaxis was nearly double that seen in other endoscopic trials that we have conducted recently, albeit within the range reported for the general population.[39] Low-dose aspirin therapy also has been associated with serious GI complications in numerous epidemiological studies.[40-43] In our study, aspirin increased the relative risk of an upper GI ulcer complication by nearly four-fold in patients on celecoxib.

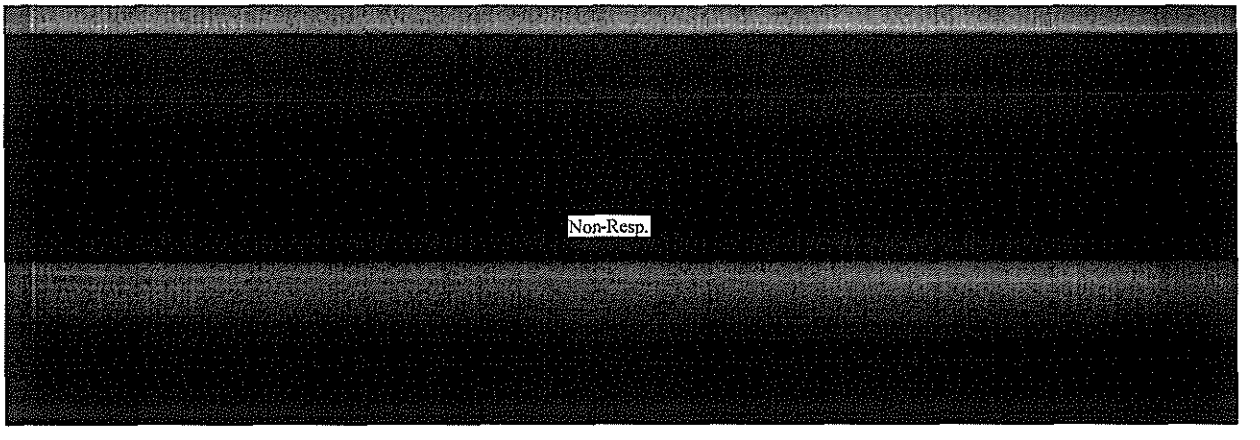
Given the confounding effect of aspirin use, analysis of the non-aspirin users in this study addresses more directly the relative upper GI safety attributes of celecoxib vs comparator NSAIDs. In this analysis, celecoxib was associated with a significantly lower incidence of upper GI ulcer complications and symptomatic ulcers vs. NSAIDs (1.40% vs 2.91%, respectively) as well as a significantly lower incidence of ulcer complications alone (0.44% vs 1.27%, respectively). The rate of ulcer complications in non-aspirin users on celecoxib (0.44%) is sufficiently close to the background rate in the population (0.1-0.4%) that the attributable risk of ulcer complications cannot be estimated with accuracy. [9;10;12;13;44-47]

In addition to the assessment of GI safety, the present study provides data to characterize the overall safety profile of celecoxib. In particular, supratherapeutic doses of celecoxib were not found to have a side effect profile that differed remarkably from the profile reported elsewhere for doses two- to four-fold lower and representing the maximum therapeutic doses for RA and OA, respectively.[33;34;48] Moreover, the incidence rates for most common and uncommon adverse effects that occurred with celecoxib were below or similar to those seen with NSAID treatment with the exception of rash and pruritus.

An important finding of the present study is that celecoxib-treated patients had a significantly lower incidence of clinically significant decreases in hemoglobin or hematocrit when compared to NSAID-treated patients, even when patients with upper GI ulcer complications, symptomatic ulcers and other cases of potential upper GI events were excluded. Such decreases with NSAIDs were also associated with evidence of decreasing iron stores. These data together suggest chronic lower GI blood loss. NSAID-associated chronic blood loss from the lower GI tract may result from two non-mutually exclusive sources: (1) pre-existing lesions (e.g. polyps) that bleed due to the anti-platelet effects of these drugs, or (2) NSAID-associated enteropathy.[49;50] Thus, the diminution of significant GI blood loss observed with celecoxib may be due to the absence of platelet effects, reduced lower GI toxicity, or both. The potential clinical implication of the decreased incidence of chronic GI blood loss with celecoxib is a reduction in the incidence of anemia, which can add to the debility of chronic arthritis or possibly exacerbate co-morbidities [redacted]Non-Resp.

Supratherapeutic doses of celecoxib were also better tolerated than NSAIDs as evidenced by the decreased incidence of GI symptoms. Improved tolerability is important clinically as reflected by the significant difference in withdrawal rates for GI symptoms. Whether or not GI symptoms are COX-1 mediated, however, is uncertain. Although ulcer complications are often asymptomatic, NSAID intolerance has been identified as a risk factor for such complications.[11;51]

The clinical consequences of NSAIDs on the kidney are heterogenous and at present the relative importance of COX-1 and COX-2 in the human kidney is not well defined.[52] Regardless, celecoxib at supratherapeutic doses appeared to be associated with significantly less renal toxicity when compared to NSAID therapy. A treatment difference was evident for increases in serum creatinine suggesting a differential effect on glomerular filtration. This observation is consistent with a recently reported renal pharmacological study in elderly subjects.[53]



In conclusion, our results establish that celecoxib at doses 2- to 4-fold greater than the maximum therapeutic doses for RA and OA is associated with reduced upper GI toxicity when compared to standard therapeutic doses of NSAIDs. This finding confirms the COX-2 hypothesis, that is, that COX-2 specific agents will exhibit diminished GI toxicity at supratherapeutic doses for OA and RA.[55] This improvement in GI safety was not tempered by other toxicities which emerged at supratherapeutic doses establishing the intrinsic safety profile of celecoxib specifically. Our findings thus have significant healthcare implications with respect to optimal drug therapy for the treatment of OA, RA and other musculoskeletal disorders.

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FIGURE LEGENDS

Figure 1: Flow chart of patient disposition

Figure 2: The annualized incidence (percentage of patients) of upper GI ulcer complications alone or combined with symptomatic gastroduodenal ulcers for the entire study population (top panel) and for the cohort of patients not taking low dose aspirin.

Figure 3: The percentage of patients with a decrease in hematocrit (Hct) of 10 percentage points or more from pretreatment, a decrease in hemoglobin (Hgb) of 2 gm/dL or more from pretreatment, or both. Results for the entire study population are shown on the left. On the right, the results for all patients excluding those with an upper GI ulcer complication, symptomatic ulcer or other diagnosed GI pathology are shown.

Figure 4: The percentage of patients with an increase in serum creatinine to a value of 2 mg/dL or more, an increase in blood urea nitrogen (BUN) to a value of 40 mg/dL, or both (top panel) and the percentage of patients with elevations in alanine aminotransferase (ALT) and asparate aminotransferase (AST) to a value three times the upper limit of normal (bottom panel).

Table 1. Definitions and Adjudication Criteria for Ulcer Complications

Event	Criteria for Confirmed Event
Gastric or duodenal perforation	A perforated lesion that required surgery. It could involve a laparoscopic repair, but only if evidence of the perforation was unequivocal, such as free air in the abdomen visible by x-ray, or peritoneal signs upon physical examination.
Gastric outlet obstruction	Gastric outlet obstruction was required to be diagnosed by the investigator, and the diagnosis was required to be supported by endoscopy (e.g., ulcer with a tight edematous pyloric channel) or by x-ray results (e.g., a dilated stomach, delayed barium emptying with clinical evidence of outlet obstruction and with an ulcer in the channel, or severe outlet narrowing and edema)

Upper GI bleeding	• hematemesis with a lesion (ulcer or large erosion) at endoscopy or x-ray
	• lesion (ulcer or large erosion) at endoscopy with evidence of active bleeding or stigmata of a recent hemorrhage (visible vessel or clot attached to the base of an ulcer)
	• melena with a lesion (ulcer or large erosion) at endoscopy or x-ray with evidence of serious bleeding, which included at least one of the following:
	  ◦ decrease in hematocrit (of at least 5 percentage points) or decrease in hemoglobin (greater than 1.5 g/dL relative to baseline)
	  ◦ signs of postural vital sign changes (increase in pulse rate of at least 20 bpm and/or decrease in systolic blood pressure of at least 20 mm Hg and/or in diastolic blood pressure of at least 10 mm Hg)
	  ◦ transfusion of more than two units of blood
	  ◦ blood in the stomach at endoscopy or nasogastric aspiration

Table 2. Baseline Characteristics and Patient Demographics

Characteristic	Celecoxib 400 mg BID (n = 3987)	NSAIDs (n = 3,981)
Mean age (range), y	60.6 (20-89)	59.8 (18-90)
>65 years of age (%)	39.1	37.3
>75 years of age (%)	12.2	11.3
Women, (%)	68.5	69.1
Race, (%)		
White	88.5	87.8
Black	7.5	8.1
Hispanic	2.7	2.8
Asian	0.8	0.7
Other	0.5	0.6
Primary disease, (%)		
RA	27.3	27.5
Mean (SD) duration of disease, y		
OA	10.2 (9.7)	10.1 (9.9)
RA	11.3 (9.9)	10.7 (9.6)
Potential Risk Factor (%)		
History of GI bleeding	1.7	1.5
History of GI ulcer	8.4	8.1
Positive *Helicobacter pylori* infection (%)	37.1	36.7
Tobacco use, (%)	15.8	14.9
Alcohol use, (%)	30.9	30.1
Concurrent medications, (%)		
Aspirin (≤325 mg daily)	20.9	20.4
Corticosteroids	30.2	29.3
Anticoagulants	0.5	0.9

Table 3. Number of Potential Cases Reported, Adjudicated Cases, Gastroduodenal Ulcers, and Ulcer Complications that Met Pre-specified Definitions

Category	Celecoxib 400 mg BID (n = 3,987)	NSAIDs (n = 3,981)
Total cases adjudicated	114	147*
Total cases not meeting the definition of a gastroduodenal ulcer or ulcer complication	82	96
Esophageal disease	16	14
Gastroduodenitis	16	19
Colonic or small bowel disease	2	6
Non-ulcer bleeding	18	21
Miscellaneous GI symptoms	24	24
Anemia	5	12
Cholelithiasis	1	-
Ulcer complications and gastroduodenal ulcers	32	51
Gastroduodenal ulcers	19	29
Ulcer complications†	13	22
Upper GI bleeding	10	20
Perforation	0	0
Gastric outlet obstruction	1	0

*p<0.001 vs celecoxib

†4 ulcer complications (2 in celecoxib patients and 2 in NSAID patients were censored from the analysis due to the timing of the event)

Table 4. Adverse Events

Characteristic	All Patients		Non-aspirin Cohort	
	Celecoxib 400 mg BID (n = 3995)	NSAIDs (n = 3987)	Celecoxib 400 mg BID (n = 3154)	NSAIDs (n = 3169)
Gastrointestinal				
Dyspepsia	14.4	18.0*	13.5	15.7*
Abdominal pain	9.7	13.1*	9.1	12.5*
Diarrhea	9.4	9.8	9.1	9.2
Nausea	6.9	9.3*	6.8	8.7*
Constipation	1.7	5.9*	1.5	5.4*
Withdrawals	10.8	13.8*	10.2	13.0*
Hepatic				
Elevated serum ALT or AST	0.9	3.2*	0.9	3.0*
Withdrawals	0.1	1.5*	0.1	1.4*
Bleeding-Related				
Anemia	2.2	4.4*	1.9	3.9*
Ecchymosis	0.7	0.8	0.7	0.8
Hematochezia	0.4	1.0*	0.3	0.9*
Withdrawals	0.3	0.6*	0.4	0.6
Renal				
Peripheral edema	2.8	3.5	2.9	3.4
Hypertension	1.7	2.3	1.5	2.0
Increased creatinine	0.7	1.2*	0.6	1.0
Withdrawals	1.2	1.0	1.2	1.0
[redacted] Non-Resp.				
Cutaneous				
Rash	5.5	2.6*	5.7	2.9*
Pruritus	2.3	1.5*	2.3	1.4*
Urticaria	0.6	0.4	0.3	0.1
Withdrawals	3.1	1.3*	3.4	1.5*

Figure 1

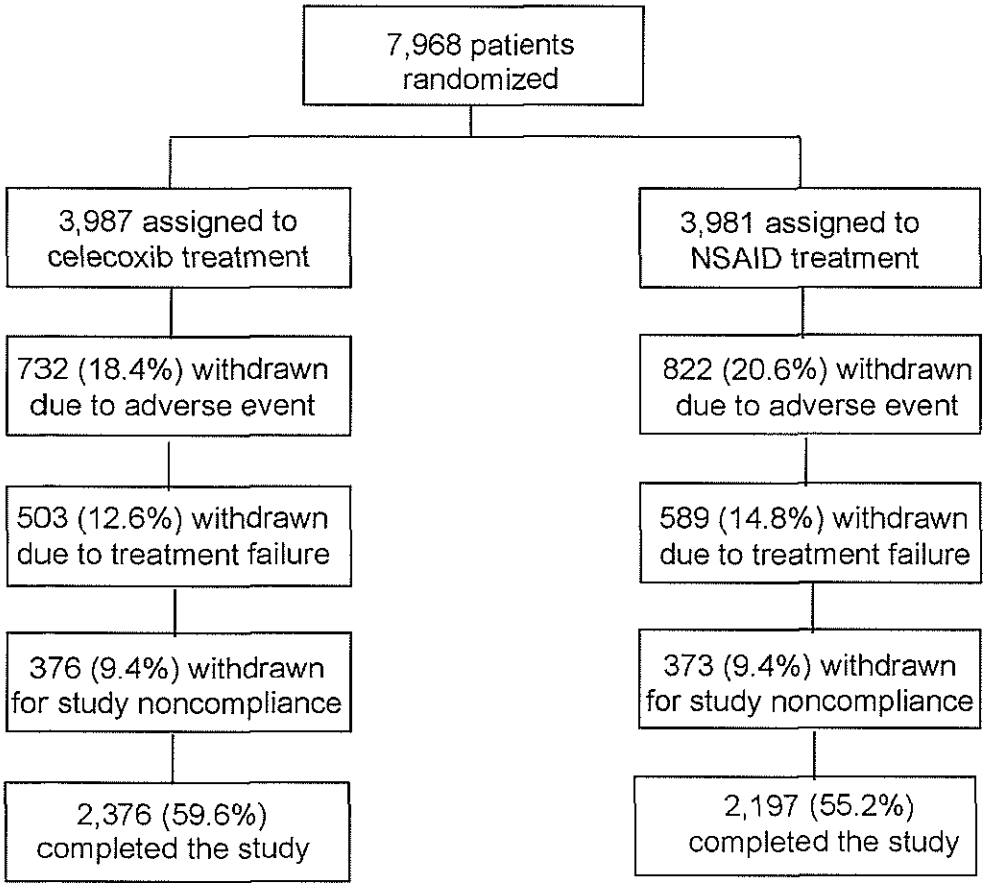
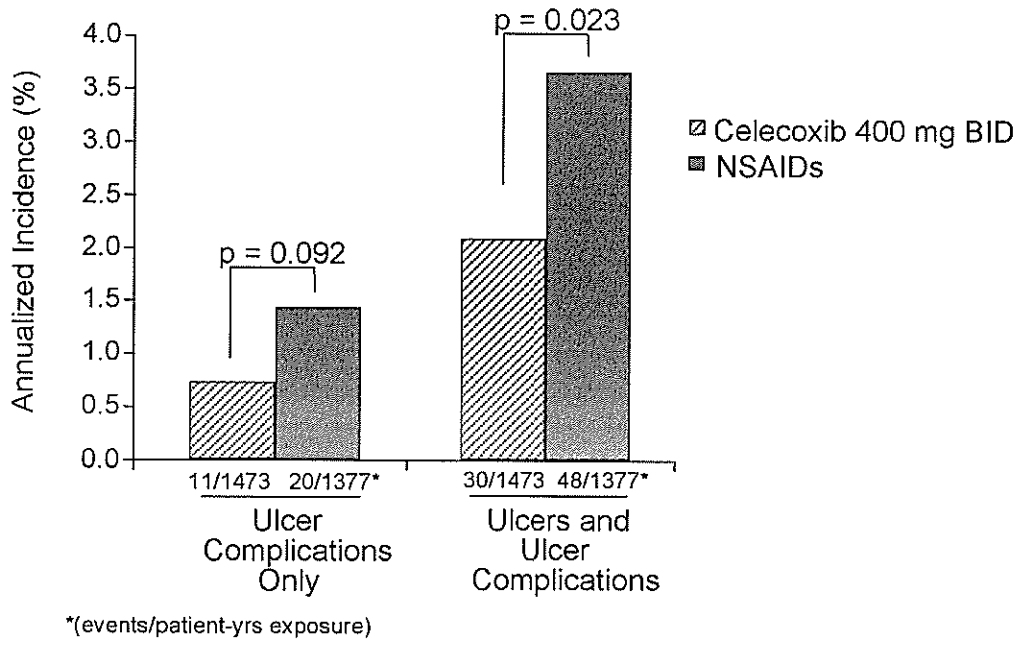

7,968 patients randomized
3,987 assigned to celecoxib treatment
3,981 assigned to NSAID treatment
732 (18.4%) withdrawn due to adverse event
822 (20.6%) withdrawn due to adverse event
503 (12.6%) withdrawn due to treatment failure
589 (14.8%) withdrawn due to treatment failure
376 (9.4%) withdrawn for study noncompliance
373 (9.4%) withdrawn for study noncompliance
2,376 (59.6%) completed the study
2,197 (55.2%) completed the study

Figure 2


Annualized Incidence (%)
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
p = 0.092
p = 0.023
11/1473 20/1377*
30/1473 48/1377*
Ulcer Complications Only
Ulcers and Ulcer Complications
Celecoxib 400 mg BID
NSAIDs
*(events/patient-yrs exposure)

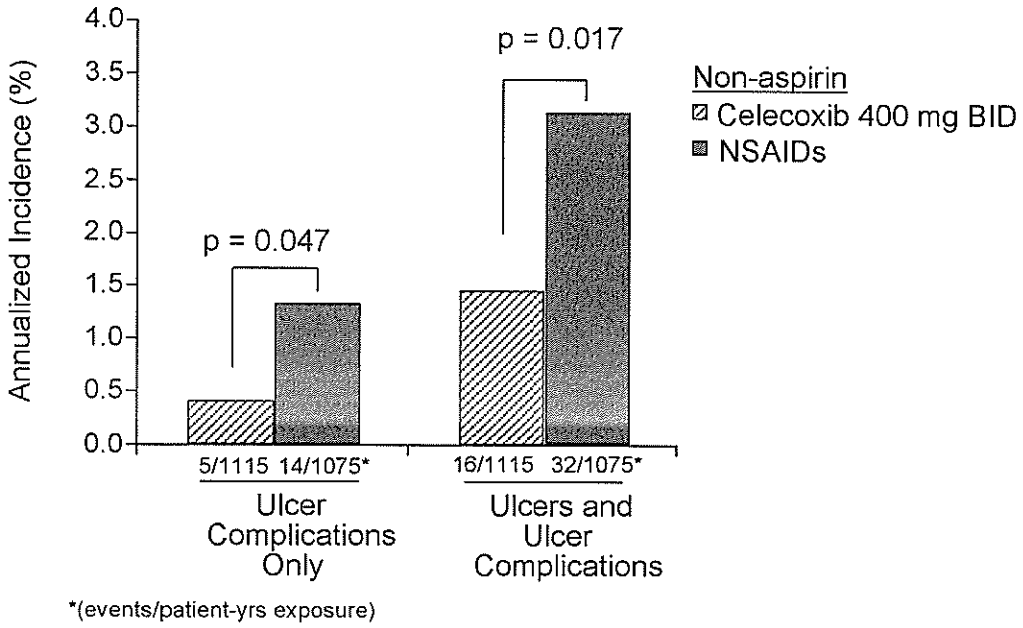

Annualized Incidence (%)
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
p = 0.047
p = 0.017
5/1115 14/1075*
16/1115 32/1075*
Ulcer Complications Only
Ulcers and Ulcer Complications
Non-aspirin
Celecoxib 400 mg BID
NSAIDs
*(events/patient-yrs exposure)

Figure 3

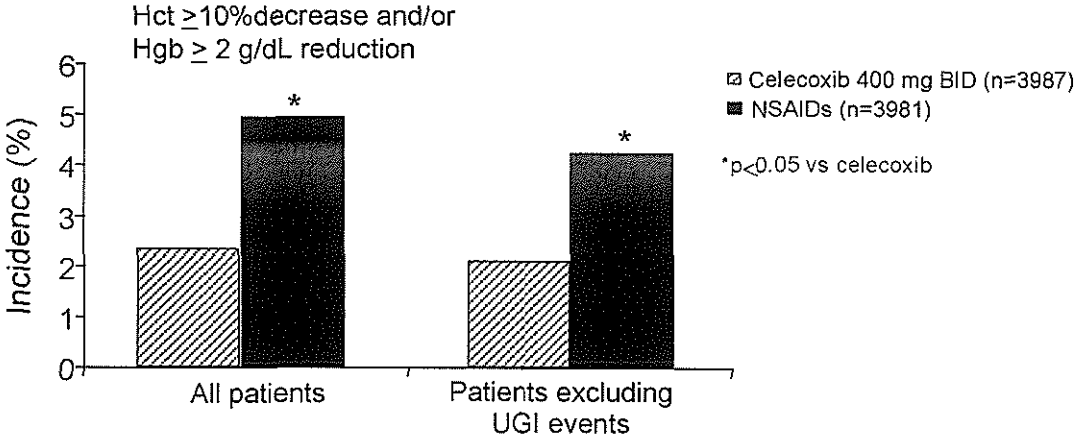
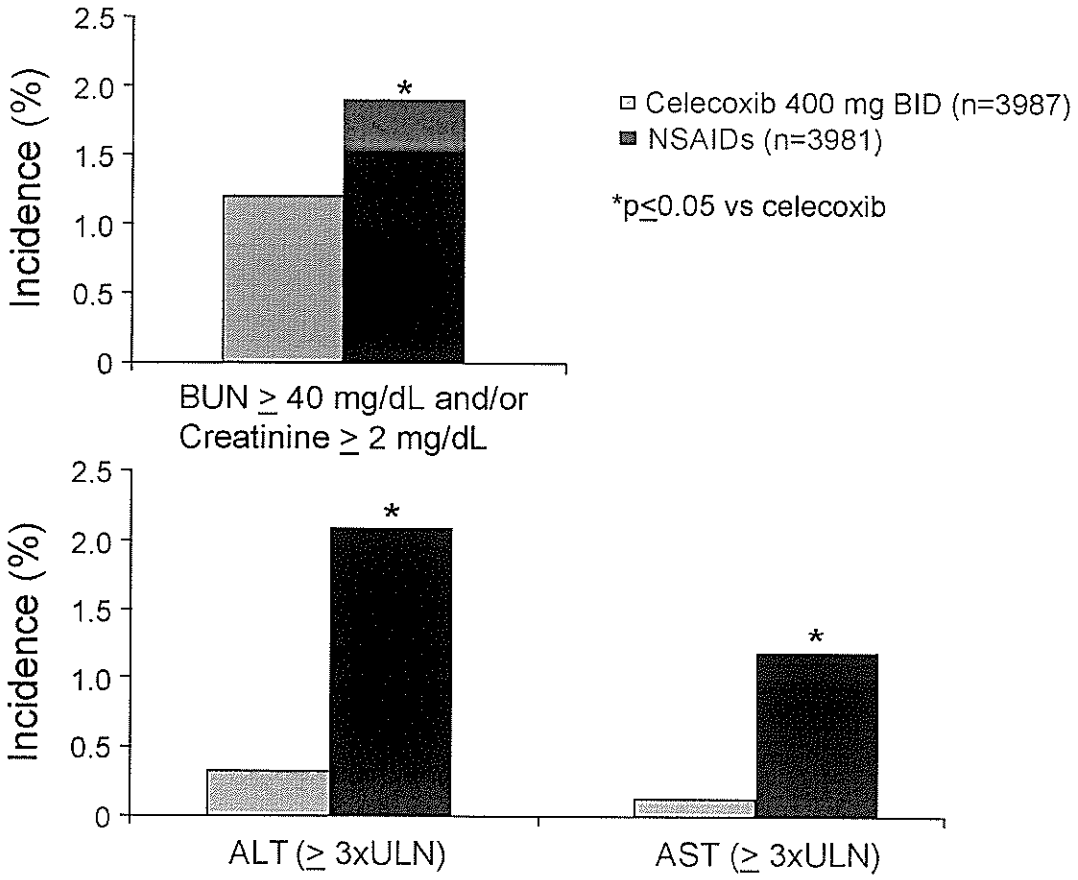

Hct ≥10%decrease and/or
Hgb ≥ 2 g/dL reduction
Incidence (%)
0
1
2
3
4
5
6
*
*
All patients
Patients excluding UGI events
Celecoxib 400 mg BID (n=3987)
NSAIDs (n=3981)
*p<0.05 vs celecoxib

Figure 4


Incidence (%)
2.5
2.0
1.5
1.0
0.5
0
*
BUN ≥ 40 mg/dL and/or
Creatinine ≥ 2 mg/dL
Celecoxib 400 mg BID (n=3987)
NSAIDs (n=3981)
*p≤0.05 vs celecoxib
Incidence (%)
2.5
2.0
1.5
1.0
0.5
0
*
*
ALT (≥ 3xULN)
AST (≥ 3xULN)

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BEGNO	ENDNO	BEGATTACH	ENDATTACH	PGS	DOCDATE	AUTHORNAM	CUSTODIAN
DEFS 00874466	DEFS 00874466	DEFS 00874466	DEFS 00874499	1	05/25/2000	LEFKOWITH, JAMES B. [PHR/1825]	Verburg, Kenneth
DEFS 00874467	DEFS 00874499	DEFS 00874466	DEFS 00874499	33	05/25/2000	Searle	Verburg, Kenneth

EXHIBIT 151

THE CELECOXIB LONG-TERM ARTHRITIS SAFETY STUDY (CLASS)

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Running Title: Upper GI Safety of Celecoxib

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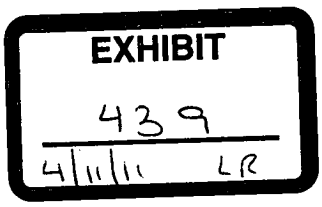
Jim, If someone criticizes us mixing up 6-month and study, are we covered ?

William



→ William

a few notes on 2, 7, 8, 11, 14, 18

THE CELECOXIB LONG-TERM ARTHRITIS SAFETY STUDY (CLASS)

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Running Title: Upper GI Safety of Celecoxib

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ABSTRACT

Context: Use of nonsteroidal anti-inflammatory drugs (NSAIDs) is associated with upper gastrointestinal (GI) toxicity caused by inhibition of GI mucosal cyclooxygenase (COX)-1. Celecoxib specifically inhibits COX-2 and has demonstrated a low potential for producing GI injury.

Objective: To compare the incidence of significant upper GI toxicity in patients with rheumatoid arthritis (RA) or osteoarthritis (OA) treated with 2- to 4-times the maximum therapeutic doses of celecoxib, respectively, versus two NSAID comparators administered at standard therapeutic doses.

Design: Randomized, multicenter, double-blind trial from October 1998 through January 2000. All patients were provided the opportunity to complete at least six months of treatment.

Setting: Three hundred eighty clinical sites in the United States and Canada.

Patients: A total of 7,968 patients aged 18 years and older with OA (n= 5,746) or RA (n= 2,183) who met inclusion criteria were randomized; 4,575 (57%) patients completed 6 months of treatment or withdrew prior to 6 months..

needs a change

didn't all 7968 complete 6 months or withdraw prior to 6 months ??

Interventions: Patients were randomized to receive celecoxib 400 mg twice daily (n=3,987), ibuprofen 800 mg three times daily (n=1,996) or diclofenac 75 mg twice daily (n=1,985) in 2:1:1 proportions. Concomitant low dose aspirin use (≤325 mg daily) for cardiovascular prophylaxis was permitted.

Main Outcome Measures: Incidence of upper GI ulcer complications (bleeding, perforation and obstruction) and symptomatic ulcers, or ulcer complications alone, for celecoxib versus NSAIDs that met pre-specified criteria judged by a blinded expert adjudication committee.

Results: For the entire cohort, the annualized incidence rates of upper GI ulcer complications alone, or combined with symptomatic ulcers, for celecoxib vs. NSAID comparators were 0.76% vs. 1.45% (p=0.092; relative risk = 0.53; 95% confidence interval (CI) 0.26 to 1.11) and 2.08% vs 3.54% (p=0.023; relative risk = 0.59; 95% CI 0.38 to 0.94). Removing the confounding effect of concomitant aspirin use, the annualized incidence rates of upper GI ulcer complications alone, or combined with symptomatic ulcers, for celecoxib vs. NSAID comparators were 0.44% vs.1.27% (p=0.037; relative risk = 0.35; 95% CI 0.14 to 0.98) and 1.40% vs 2.91% (p=0.017; relative risk = 0.48; 95% CI 0.28 to 0.89). Overall, celecoxib was better tolerated than NSAID comparators as fewer celecoxib-treated patients experienced GI, hepatic, renal or hemostasis-related adverse effects. [redacted] Non-Resp. [redacted] Non-Resp.

Conclusion: Celecoxib, at 2- to 4-times the maximally effective RA and OA doses, was associated with a lower incidence of significant upper GI toxicity and other adverse effects than NSAID comparators at standard therapeutic doses. This study validates celecoxib's unique mechanism of action and intrinsic general safety profile.

Key words: ulcer complications, symptomatic ulcers, cyclooxygenase, NSAIDs, celecoxib

Word Count: 3730 (manuscript), 431 (abstract)

INTRODUCTION

Musculoskeletal disorders are extremely common and represent a frequent cause of health care resource utilization.[1] For such disorders, nonsteroidal anti-inflammatory drugs (NSAIDs) are a mainstay of clinical care and are the preferred agent by patients.[2-4] Well-established limitations of NSAID therapy include the risk of developing significant injury to the upper gastrointestinal (GI) tract, primarily ulceration or complications resulting from an ulcer such as perforation, gastric outlet obstruction and hemorrhage. Based on epidemiological and controlled trial experience, there is an estimated two- to ten-fold greater risk for upper GI injury in NSAID users when compared to nonusers.[5-11] The annualized incidence rate of upper GI ulcer complications and symptomatic ulcers in NSAID users ranges from 2 to 4% and 1 to 2% for ulcer complications alone.[12-16]

It is known that NSAIDs inhibit cyclooxygenase (COX), the enzyme responsible for the conversion of arachidonic acid to prostaglandins.[17] The ulcerogenic effects of these agents are attributed to interference with prostaglandin formation, thereby, leading to inadequate mucosal protection in the upper GI tract.[18;19] COX exists in two isoforms.[20-23] COX-1 is a ubiquitous constitutive isozyme; both gastrointestinal prostaglandins and platelet-derived thromboxane A_2 are formed exclusively from COX-1. Alternatively, COX-2 is largely a cytokine-induced isozyme producing prostaglandins that mediate pain and inflammation.[24-30] NSAIDs inhibit both COX-1 and COX-2 to varying degrees.[31;32] Thus, the therapeutic effects of NSAIDs are derived from inhibition of COX-2, while the adverse effects of these agents within the upper GI tract or with respect to platelet function arise from inhibition of COX-1 activity.

Celecoxib (Celebrex) is a recently approved agent for treating the inflammation and pain of arthritis that specifically inhibits COX-2. Celecoxib appears to have little potential to produce upper GI injury as evidenced by a four-fold to six-fold lower association with gastroduodenal ulceration than either naproxen or diclofenac in endoscopic studies.[33;34] In these same trials, the risk of gastroduodenal ulceration in celecoxib-treated patients was comparable to placebo. A pooled analysis of 14 randomized controlled trials of arthritis patients also indicated that the incidence of upper GI ulcer complications associated with celecoxib was eight-fold lower than that found with diclofenac, ibuprofen and naproxen combined.[16]

In order to establish the distinct nature of the underlying biochemical mechanism of celecoxib more rigorously, however, it was essential to perform a prospective, randomized, double-blind study to determine the incidence of upper GI ulcer complications alone or combined with symptomatic gastroduodenal ulcers among arthritis patients chronically receiving celecoxib or NSAIDs. To clearly establish that celecoxib is COX-1 sparing, our study compared celecoxib administered at 2- to 4-times the maximum effective doses for RA and OA, respectively, to common therapeutic doses of ibuprofen and diclofenac, two non-specific NSAIDs commonly used to treat OA and RA. Concomitantly, this study served to assess more broadly the safety of celecoxib at supratherapeutic doses with respect to other potentially mechanism-based, as well as idiosyncratic, toxicities.

METHODS

Study Population

Men and women outpatients 18 years of age and older were eligible to participate in the study they were diagnosed with OA or RA evident for 3 months or longer and were expected to require continuous treatment with an NSAID for the duration of the trial. Patients were excluded from the study participation if they had active GI, renal, hepatic, or coagulation disorders; malignancy (unless removed surgically with no recurrence within 5 years); esophageal or gastroduodenal ulceration within the previous 30 days; a history of gastric or duodenal surgery other than an oversew; or known hypersensitivity to COX-2 inhibitors, sulfonamides, ibuprofen, or diclofenac. Women were excluded if they were pregnant, might become pregnant, or were lactating.

Study Protocol

This prospective, randomized, double-blind trial was conducted at 380 centers in the United States and Canada from December 1998 to January 2000 in accordance with the principles of good clinical practice and the Declaration of Helsinki. The protocol was approved by the institutional review board at each study site and all patients were required to provide written informed consent.

Prior to enrollment, patients completed a physical examination and clinical laboratory testing, including a baseline serological test for *Helicobacter pylori* antibodies (FlexSure, Beckman-Coulter, Palo Alto, CA). After a baseline visit, follow-up clinic visits took place at weeks 4, 13, 26, and every 13 weeks thereafter (if necessary) after the initial dose of medication.

Jim.
Some comments on the CLASS article
Carl

ABSTRACT

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Main Outcome Measures: Incidence of upper GI ulcer complications (bleeding, perforation and obstruction) and symptomatic ulcers, or ulcer complications alone, for celecoxib versus NSAIDs that met pre-specified criteria judged by a blinded expert adjudication committee.

Monitoring for adverse events and clinical laboratory testing were repeated at all follow-up visits. All patients were given the opportunity to complete a minimum of 6 months of treatment.

Treatment

Patients were randomly assigned by a computer-generated randomization schedule to receive either celecoxib 400 mg BID or the comparator NSAID (ibuprofen 800 mg TID or diclofenac 75 mg BID) on a 2:1:1 basis. All treatment regimens were fully masked to ensure they were identical in appearance and that patients took the same number of capsules.

Concomitant Medications

NSAIDs (except for stables doses of aspirin up to 325 mg daily); anti-ulcer drugs (except for single dose antacid use daily or multiple dose use up to 7 days each month); antibiotics used alone or in combination with omeprazole, lansoprazole, and ranitidine for treatment of *H. pylori* infection; and antineoplastics were prohibited during the course of the study. Use of oral, intramuscular, and intra-articular corticosteroids, and DMARDs were permitted.

was

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Clinical Assessments

Investigators were instructed to identify and report all potential upper GI ulcer complications. Evaluation of such events was outlined in a pre-specified algorithm structured to reproduce clinical practice norms. Evaluation was required for any of the following presentations: severe acute abdominal pain or acute abdomen; intractable abdominal pain with nausea or vomiting; hematemesis or melena; acute hypovolemia or hypotension; history of melena within the past

this difference with a 5% significance level (two-sided) and a power of 85% and assuming a 30% withdrawal rate, a sample size of approximately 4,000 patients was required for the celecoxib group and 2,000 patients for each NSAID group. ?

Homogeneity of the treatment groups at baseline was analyzed by using the chi-square test for categorical variables and two-way ANOVA with treatment and center effects for continuous variables. All statistical analyses were conducted on the intent-to-treat populations that consisted of all patients who received at least one dose of assigned study medication. Except the subgroup not receiving aspirin was used for numerous analyses since ASA was such an important risk factor Time-to-event analyses of upper GI ulcer complications alone or combined with symptomatic ulcers were performed based on Kaplan-Meier estimates of cumulative event rates, but are expressed in the text as annualized incidence rates. Log-rank tests were used to compare the ~~incidence~~ time to event curves between treatments. ~~rates based on the Kaplan-Meier estimate~~. The effects of potential risk factors for the development of an ulcer complication (including but not limited to concurrent aspirin use) were ~~pre-specified and~~ analyzed by Cox proportional hazards model. Treatment-related differences in the incidence of adverse effects or clinical laboratory changes were determined by Fisher's exact test.

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gastroduodenal ulcers (Table 3). All but one of the upper GI ulcer complications (a gastric outlet obstruction in a celecoxib-treated patient) represented bleeding events in which an ulcer or large erosion was associated with either visual evidence of bleeding, melena, or occult blood-positive stools and a decrease in hematocrit or hemoglobin. Four upper GI ulcer complications (2 in celecoxib patients and 2 in NSAID-treated patients) were censored from the analysis owing to the timing of the event as prespecified by the Events Committee (within 48 hours after the first dose day or after 14 days after the last known dose). The remaining 178 cases were judged by the Committee to represent neither an upper GI ulcer complication nor a symptomatic ulcer and were assigned a diagnosis under the categories listed in Table 3.

The annualized incidence of upper GI ulcer complications in celecoxib-treated patients based on 6 months exposure was approximately one-half the rate observed in patients taking NSAIDs (0.76% vs 1.45%, p=0.092, Figure 2 top panel). The relative risk over 6 months for celecoxib compared to NSAIDs was 0.53 (95% CI, 0.26-1.11). The annualized incidence of upper GI ulcer complications plus symptomatic ulcers with celecoxib was significantly lower than with NSAIDs (2.08% vs 3.54%, p=0.023, Figure 2 top panel). The relative risk over 6 months for celecoxib compared to NSAIDs was 0.59 (95% CI, 0.38-0.94).

time-to-event ?

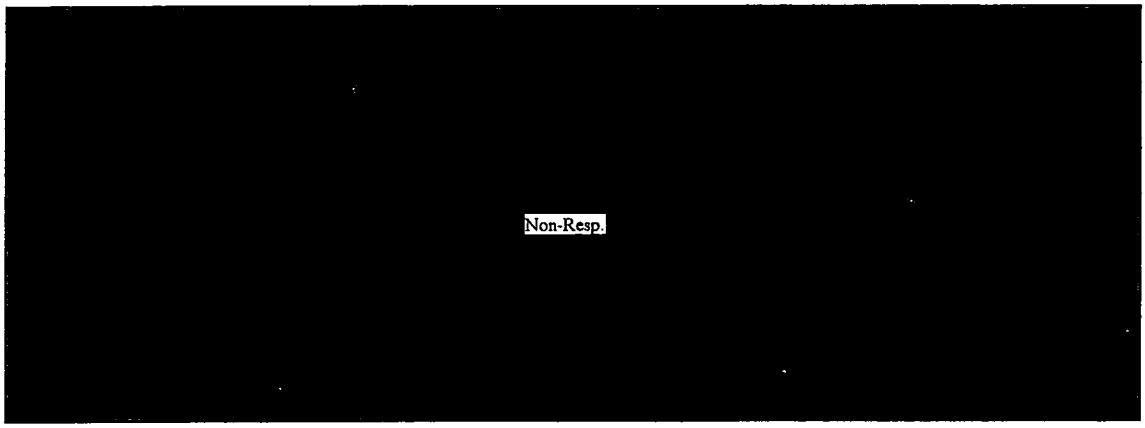
Based on survival analyses with a Cox proportional hazard model, low dose aspirin use was found to have a statistically significant effect (p=0.005) on the incidence of upper GI ulcer complications (alone or in combination with symptomatic ulcers) in the celecoxib-treated patients. Within the celecoxib treatment group, an upper GI ulcer complication was nearly 4-fold more common in aspirin users occurring in 6 of 833 patients (0.7%) taking low dose

elevated serum creatinine was noted more frequently by investigators in patients on NSAIDs than in patients on celecoxib ($p<0.05$). Also, a greater number of patients ($p<0.05$) receiving NSAIDs were found with elevations in serum creatinine levels above 2 mg/dL and/or BUN values above 40 mg /dL than with celecoxib (Figure 4). Celecoxib was associated with a significantly higher incidence ($p<0.05$) of rash and pruritus and study withdrawals due to cutaneous adverse effects as compared to NSAID therapy (Table 4). [redacted] Non-Resp. [redacted] Non-Resp. [redacted] No treatment differences in such events were apparent in the patients ~~in the two treatment groups~~ not really necessary not taking aspirin for cardiovascular prophylaxis (Table 4).

Serious adverse effects (representing hospitalizations or malignancies detected during study participation) were reported for 4.3% of patients receiving celecoxib and 4.2% of NSAID patients. The most common serious adverse effects were accidental fractures, pneumonia, [redacted] Non-Resp. [redacted] consistent with expected co-morbidities in this patient population. No serious rashes or unexpected serious adverse events were observed in patients on celecoxib. No treatment-related differences were observed.

Supratherapeutic doses of celecoxib were also better tolerated than NSAIDs as evidenced by the decreased incidence of GI symptoms. Improved tolerability is important clinically as reflected by the significant ~~difference in~~ lower withdrawal rates for GI symptoms among the celecoxib groups. Whether or not GI symptoms are COX-1 mediated, however, is uncertain. Although ulcer complications are often asymptomatic, NSAID intolerance has been identified as a risk factor for such complications.[11;51]

The clinical consequences of NSAIDs on the kidney are heterogenous and at present the relative importance of COX-1 and COX-2 in the human kidney is not well defined.[52] Regardless, celecoxib at supratherapeutic doses appeared to be associated with significantly less renal toxicity when compared to NSAID therapy. A treatment difference was evident for increases in serum creatinine, higher incidence with NSAIDs, suggesting a differential effect on glomerular filtration. This observation is consistent with a recently reported renal pharmacological study in elderly subjects.[53]



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14 days or black stool representing a change in normal pattern; development of postural dizziness or lightheadedness, or syncope; history of vaguely characterized dark stool, or dark stool within the past 14 days or with concurrent iron or bismuth ingestion; history of hematochezia, or anal or rectal bleeding after elimination; development of new anemia or decrease in hematocrit of 5% of more; development of dyspepsia, abdominal pain, or nausea or vomiting; or development of heme-positive stools. Endoscopy was encouraged to document bleeding lesions but could also be performed if indicated by the investigator's clinical judgement.

All documentation relating to potential ulcer complications was forwarded to a Gastrointestinal Events Committee (comprised of Jay Goldstein, MD, Naurang Agrawal, MD, Glenn Eisen, MD, and William Stenson, MD). The Committee was established to review and adjudicate all potential events according to prospectively established upper GI ulcer complication definitions as provided in Table 1. The Committee collectively reviewed each case in a blinded fashion and assigned it by consensus as either meeting or not meeting the definition of an upper GI ulcer complication. Symptomatic ulcers comprised those cases that did not meet the definition of an ulcer complication, but did have endoscopic or x-ray evidence of a gastric or duodenal ulcer as judged by the Committee. All patients with symptomatic ulcers or ulcer complications were withdrawn from the study.

Statistical Analysis

The sample size calculations were based on the assumption that the annualized incidence of upper GI ulcer complications would be 0.3% for celecoxib and 1.2% for NSAIDs. To detect

this difference with a 5% significance level (two-sided) and a power of 85% and assuming a 30% withdrawal rate, a sample size of approximately 4,000 patients was required for the celecoxib group and 2,000 patients for each NSAID group. ?

Homogeneity of the treatment groups at baseline was analyzed by using the chi-square test for categorical variables and two-way ANOVA with treatment and center effects for continuous variables. All statistical analyses were conducted on the intent-to-treat populations that consisted of all patients who received at least one dose of assigned study medication (except the subgroup not receiving aspirin was used for numerous analyses since ASA is such an important risk factor). Time-to-event analyses of upper GI ulcer complications alone or combined with symptomatic ulcers were performed based on Kaplan-Meier estimates of cumulative event rates, but are expressed in the text as annualized incidence rates. Log-rank tests were used to compare the ~~incidence~~ time to event curves between treatments. ~~rates based on the Kaplan-Meier estimate~~. The effects of potential risk factors for the development of an ulcer complication (including but not limited to concurrent aspirin use) were ~~pre-specified and~~ analyzed by Cox proportional hazards model. Treatment-related differences in the incidence of adverse effects or clinical laboratory changes were determined by Fisher's exact test.

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RESULTS

A total of 7,968 patients were enrolled. Of these, 3,987 patients were treated with celecoxib 400 mg BID and 3,981 patients were treated with NSAIDs (1,996 received ibuprofen 800 mg TID and 1,985 received diclofenac 75 mg BID). Total patient-years of exposure were 1,473 and 1,377 in the celecoxib and NSAID treatment groups, respectively. There were no clinically meaningful differences in baseline characteristics between groups (Table 2). Mean age overall was 60 years (range 18-90 years); 38% of the patients were 65 years or older, 69% were women and 73% were diagnosed with OA. Approximately, 10% of the patients in each group had a prior medical history of a peptic ulcer or upper GI bleeding and over 20% of the patients were taking low dose aspirin ($\leq$325 mg daily) for cardiovascular prophylaxis. Approximately 57% of the patients (n=4,573) completed six months of treatment. Figure 1 shows reasons for early discontinuation from the study. More patients in the NSAID treatment group withdrew from the study for either adverse effects or for lack of efficacy than did celecoxib-treated patients ($p<0.05$). No patients were lost to follow-up.

The crude rate of potential upper GI ulcer complications reported by investigators to the Events Committee over 6 months was significantly lower in celecoxib-treated patients than with NSAIDs (16.0% vs 12.6%, $p<0.001$). All reports were reviewed by the Events Committee and a total of 261 cases of potential upper GI ulcer complications were selected for adjudication (the remainder being cases of either isolated GI symptoms or anemia without further evidence of a potential event). Upon adjudication, the Events Committee identified 35 upper GI ulcer complications and another 48 cases that represented symptomatic, but uncomplicated,

gastroduodenal ulcers (Table 3). All but one of the upper GI ulcer complications (a gastric outlet obstruction in a celecoxib-treated patient) represented bleeding events in which an ulcer or large erosion was associated with either visual evidence of bleeding, melena, or occult blood-positive stools and a decrease in hematocrit or hemoglobin. Four upper GI ulcer complications (2 in celecoxib patients and 2 in NSAID-treated patients) were censored from the analysis owing to the timing of the event as prespecified by the Events Committee (within 48 hours after the first dose day or after 14 days after the last known dose). The remaining 178 cases were judged by the Committee to represent neither an upper GI ulcer complication nor a symptomatic ulcer and were assigned a diagnosis under the categories listed in Table 3.

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aspirin vs 5 such events in 3,154 (0.2%) non-aspirin users. Low dose aspirin use did not have a significant effect on the rate of upper GI ulcer complications in patients receiving NSAIDs (p=0.21). In consequence, the non-aspirin using cohort was examined independently.

The annualized incidence of upper GI ulcer complications over 6 months in non-aspirin users was significantly lower with celecoxib vs NSAIDs (0.44% vs 1.27%, p=0.037, Figure 2 bottom panel). The relative risk over 6 months for celecoxib compared to NSAIDs was 0.35 (95% CI, 0.14-0.98). The annualized incidence of upper GI ulcer complications plus symptomatic ulcers over 6 months in patients not taking aspirin users was also significantly lower with celecoxib than with NSAIDs (1.40% vs 2.91%, p=0.017, Figure 2 bottom panel). The relative risk over 6 months for celecoxib compared to NSAIDs was 0.48 (95% CI, 0.28-0.89).

Celecoxib, administered at 2- to 4-times the maximum effective RA and OA doses respectively, was safe and generally well-tolerated when chronically administered as compared to standard therapeutic doses of either ibuprofen or diclofenac. The adverse effects with the highest incidence in either treatment group were dyspepsia, upper respiratory infection, headache, abdominal pain and diarrhea.

Celecoxib was associated with better GI tolerability than NSAID treatment. The overall incidence of GI adverse effects experienced by patients taking celecoxib was significantly lower than with NSAIDs (40% vs 45%; p<0.001) as was the rate of withdrawal due to GI intolerability (Table 4). Of the most commonly reported GI adverse effects, dyspepsia, abdominal pain, nausea, and constipation were significantly less common (p<0.001) with

celecoxib than with NSAIDs (Table 4). Similar effects were seen in the cohort of patients not taking low dose aspirin.

Significantly less hemostasis-related adverse effects (anemia, ecchymoses, hematochezia) and withdrawals due to such were observed in patients receiving celecoxib when compared to NSAID-treated patients (Table 4). Celecoxib was also associated with a lower incidence ($p<0.05$) of clinically meaningful reductions in hematocrit or hemoglobin for the entire patient cohort (Figure 3). This difference persisted when all patients with potential upper GI events were excluded from the analysis, thus removing all patients with ulcer complications, symptomatic ulcers or other diagnosed GI pathology (Figure 3). In parallel with changes seen in hematocrit and hemoglobin, serum iron to iron binding capacity ratios tended to increase on celecoxib and decrease on NSAIDs (+1.4% vs -2.4%, $p<0.05$).

As shown in Figure 4, the incidence of serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevations that exceeded 3 times the upper limit of normal was 5- to 10-fold higher ($p<0.05$) in patients receiving NSAIDs than with celecoxib. Similarly, investigators reported a significantly higher ($p<0.05$) incidence of elevated serum transaminases with NSAID treatment (Table 4). Study withdrawals due to elevated serum transaminases were also higher in patients receiving NSAIDs. Most liver function enzyme elevations occurred in patients receiving diclofenac.

The incidence rates of renal-related adverse effects such as peripheral edema, [redacted] were similar between the treatment groups (Table 4). However, an

elevated serum creatinine was noted more frequently by investigators in patients on NSAIDs than in patients on celecoxib ($p<0.05$). Also, a greater number of patients ($p<0.05$) receiving NSAIDs were found with elevations in serum creatinine levels above 2 mg/dL and/or BUN values above 40 mg /dL than with celecoxib (Figure 4). Celecoxib was associated with a significantly higher incidence ($p<0.05$) of rash and pruritus and study withdrawals due to cutaneous adverse effects as compared to NSAID therapy (Table 4). [redacted] Non-Resp. [redacted] Non-Resp. No treatment differences in such events were apparent in the patients in the two treatment groups not taking aspirin for cardiovascular prophylaxis (Table 4).

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DISCUSSION

Our study establishes that celecoxib when used chronically at 2- to 4-times the maximum effective doses for RA and OA, respectively, is associated with a lower incidence of upper GI ulcer complications and symptomatic ulcers than comparator NSAIDs (ibuprofen and diclofenac) at standard therapeutic doses. This study thus directly addresses the critical safety issue inherent to COX-2 specificity, namely that COX-2 specific inhibitors are associated with a reduction in upper GI toxicity relative to non-specific COX inhibitors. In addition, the data presented herein support the overall safety and tolerability of celecoxib, part of which may be mechanism-dependent and part of which may be specific to the pharmacology of this agent. It is worth noting that a clinical trial using an NSAID at supratherapeutic doses (similar to those used for celecoxib in the current trial) would not be feasible given the known toxicology of NSAIDs.[35-38]

The driving force behind the development of COX-2 specific inhibitors has been a widening appreciation of the mechanism-based GI toxicity of NSAIDs. The public health impact of NSAID-related upper GI toxicity is substantial. Based on the NSAID-attributable incidence of ulcer complications, it has been estimated that such complications lead to approximately 107,000 hospitalizations and 16,500 deaths yearly in the US.[11]

In this study, the incidence of an upper GI ulcer complication combined with symptomatic ulcers associated with NSAID comparators was 3.54%, with an incidence of ulcer complication alone of 1.45%. In comparison, the corresponding rates associated with supratherapeutic doses of celecoxib in this study were 2.08% and 0.76%, respectively, the difference in

symptomatic ulcers and ulcer complications being statistically significant. The lack of a statistical significant separation of upper GI complications associated with celecoxib when compared to NSAIDs in the entire study cohort was largely a function of the higher than expected event rate observed in the celecoxib treatment group relative to the previously reported annualized incidence rate of 0.2% obtained from a pooled analyses of 14 randomized controlled trials ranging from 2 to 24 weeks in duration.[16]

This increase was attributable to concurrent low-dose aspirin use. The percentage of patients using low-dose aspirin for cardiovascular prophylaxis was nearly double that seen in other endoscopic trials that we have conducted recently, albeit within the range reported for the general population.[39] Low-dose aspirin therapy also has been associated with serious GI complications in numerous epidemiological studies.[40-43] In our study, aspirin increased the relative risk of an upper GI ulcer complication by nearly four-fold in patients on celecoxib.

Given the confounding effect of aspirin use, analysis of the non-aspirin users in this study addresses more directly the relative upper GI safety attributes of celecoxib vs comparator NSAIDs. In this analysis, celecoxib was associated with a significantly lower incidence of upper GI ulcer complications and symptomatic ulcers vs. NSAIDs (1.40% vs 2.91%, respectively) as well as a significantly lower incidence of ulcer complications alone (0.44% vs 1.27%, respectively). The rate of ulcer complications in non-aspirin users on celecoxib (0.44%) is sufficiently close to the background rate in the population (0.1-0.4%) that the attributable risk of ulcer complications cannot be estimated with accuracy. [9;10;12;13;44-47]

In addition to the assessment of GI safety, the present study provides data to characterize the overall safety profile of celecoxib. In particular, supratherapeutic doses of celecoxib were not found to have a side effect profile that differed remarkably from the profile reported elsewhere for doses two- to four-fold lower and representing the maximum therapeutic doses for RA and OA, respectively.[33;34;48] Moreover, the incidence rates for most common and uncommon adverse effects that occurred with celecoxib were below or similar to those seen with NSAID treatment with the exception of rash and pruritus.

An important finding of the present study is that celecoxib-treated patients had a significantly lower incidence of clinically significant decreases in hemoglobin or hematocrit when compared to NSAID-treated patients, even when patients with upper GI ulcer complications, symptomatic ulcers and other cases of potential upper GI events were excluded. Such decreases with NSAIDs were also associated with evidence of decreasing iron stores. These data together suggest chronic lower GI blood loss. NSAID-associated chronic blood loss from the lower GI tract may result from two non-mutually exclusive sources: (1) pre-existing lesions (e.g. polyps) that bleed due to the anti-platelet effects of these drugs, or (2) NSAID-associated enteropathy.[49;50] Thus, the diminution of significant GI blood loss observed with celecoxib may be due to the absence of platelet effects, reduced lower GI toxicity, or both. The potential clinical implication of the decreased incidence of chronic GI blood loss with celecoxib is a reduction in the incidence of anemia, which can add to the debility of chronic arthritis or possibly exacerbate co-morbidities [redacted] Non-Resp.

Supratherapeutic doses of celecoxib were also better tolerated than NSAIDs as evidenced by the decreased incidence of GI symptoms. Improved tolerability is important clinically as reflected by the significant ~~difference in~~ lower withdrawal rates for GI symptoms among the celecoxib groups. Whether or not GI symptoms are COX-1 mediated, however, is uncertain. Although ulcer complications are often asymptomatic, NSAID intolerance has been identified as a risk factor for such complications.[11;51]

The clinical consequences of NSAIDs on the kidney are heterogenous and at present the relative importance of COX-1 and COX-2 in the human kidney is not well defined.[52] Regardless, celecoxib at supratherapeutic doses appeared to be associated with significantly less renal toxicity when compared to NSAID therapy. A treatment difference was evident for increases in serum creatinine, higher incidence with NSAIDs, suggesting a differential effect on glomerular filtration. This observation is consistent with a recently reported renal pharmacological study in elderly subjects.[53]

[redacted]
Non-Resp.

In conclusion, our results establish that celecoxib at doses 2- to 4-fold greater than the maximum therapeutic doses for RA and OA is associated with reduced upper GI toxicity when compared to standard therapeutic doses of NSAIDs. This finding confirms the COX-2 hypothesis, that is, that COX-2 specific agents will exhibit diminished GI toxicity at supratherapeutic doses for OA and RA.[55] This improvement in GI safety was not tempered by other toxicities which emerged at supratherapeutic doses establishing the intrinsic safety profile of celecoxib specifically. Our findings thus have significant healthcare implications with respect to optimal drug therapy for the treatment of OA, RA and other musculoskeletal disorders.

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FIGURE LEGENDS

Figure 1: Flow chart of patient disposition

Figure 2: The annualized incidence (percentage of patients) of upper GI ulcer complications alone or combined with symptomatic gastroduodenal ulcers for the entire study population (top panel) and for the cohort of patients not taking low dose aspirin.

Figure 3: The percentage of patients with a decrease in hematocrit (Hct) of 10 percentage points or more from pretreatment, a decrease in hemoglobin (Hgb) of 2 gm/dL or more from pretreatment, or both. Results for the entire study population are shown on the left. On the right, the results for all patients excluding those with an upper GI ulcer complication, symptomatic ulcer or other diagnosed GI pathology are shown.

Figure 4: The percentage of patients with an increase in serum creatinine to a value of 2 mg/dL or more, an increase in blood urea nitrogen (BUN) to a value of 40 mg/dL, or both (top panel) and the percentage of patients with elevations in alanine aminotransferase (ALT) and asparate aminotransferase (AST) to a value three times the upper limit of normal (bottom panel).

Table 1. Definitions and Adjudication Criteria for Ulcer Complications

Event	Criteria for Confirmed Event
Gastric or duodenal perforation	A perforated lesion that required surgery. It could involve a laparoscopic repair, but only if evidence of the perforation was unequivocal, such as free air in the abdomen visible by x-ray, or peritoneal signs upon physical examination.
Gastric outlet obstruction	Gastric outlet obstruction was required to be diagnosed by the investigator, and the diagnosis was required to be supported by endoscopy (e.g., ulcer with a tight edematous pyloric channel) or by x-ray results (e.g., a dilated stomach, delayed barium emptying with clinical evidence of outlet obstruction and with an ulcer in the channel, or severe outlet narrowing and edema)

Upper GI bleeding	• hematemesis with a lesion (ulcer or large erosion) at endoscopy or x-ray
	• lesion (ulcer or large erosion) at endoscopy with evidence of active bleeding or stigmata of a recent hemorrhage (visible vessel or clot attached to the base of an ulcer)
	• melena with a lesion (ulcer or large erosion) at endoscopy or x-ray with evidence of serious bleeding, which included at least one of the following:
	  • decrease in hematocrit (of at least 5 percentage points) or decrease in hemoglobin (greater than 1.5 g/dL relative to baseline)
	  • signs of postural vital sign changes (increase in pulse rate of at least 20 bpm and/or decrease in systolic blood pressure of at least 20 mm Hg and/or in diastolic blood pressure of at least 10 mm Hg)
	  • transfusion of more than two units of blood
	  • blood in the stomach at endoscopy or nasogastric aspiration

Table 2. Baseline Characteristics and Patient Demographics

Characteristic	Celecoxib 400 mg BID (n = 3987)	NSAIDs (n = 3,981)
Mean age (range), y	60.6 (20-89)	59.8 (18-90)
>65 years of age (%)	39.1	37.3
>75 years of age (%)	12.2	11.3
Women, (%)	68.5	69.1
Race, (%)		
White	88.5	87.8
Black	7.5	8.1
Hispanic	2.7	2.8
Asian	0.8	0.7
Other	0.5	0.6
Primary disease, (%)		
RA	27.3	27.5
Mean (SD) duration of disease, y		
OA	10.2 (9.7)	10.1 (9.9)
RA	11.3 (9.9)	10.7 (9.6)
Potential Risk Factor (%)		
History of GI bleeding	1.7	1.5
History of GI ulcer	8.4	8.1
Positive *Helicobacter pylori* infection (%)	37.1	36.7
Tobacco use, (%)	15.8	14.9
Alcohol use, (%)	30.9	30.1
Concurrent medications, (%)		
Aspirin (≤325 mg daily)	20.9	20.4
Corticosteroids	30.2	29.3
Anticoagulants	0.5	0.9

Table 3. Number of Potential Cases Reported, Adjudicated Cases, Gastroduodenal Ulcers, and Ulcer Complications that Met Pre-specified Definitions

Category	Celecoxib 400 mg BID (n = 3,987)	NSAIDs (n = 3,981)
Total cases adjudicated	114	147*
Total cases not meeting the definition of a gastroduodenal ulcer or ulcer complication	82	96
Esophageal disease	16	14
Gastroduodenitis	16	19
Colonic or small bowel disease	2	6
Non-ulcer bleeding	18	21
Miscellaneous GI symptoms	24	24
Anemia	5	12
Cholelithiasis	1	-
Ulcer complications and gastroduodenal ulcers	32	51
Gastroduodenal ulcers	19	29
Ulcer complications†	13	22
Upper GI bleeding	10	20
Perforation	0	0
Gastric outlet obstruction	1	0

*p<0.001 vs celecoxib

†4 ulcer complications (2 in celecoxib patients and 2 in NSAID patients were censored from the analysis due to the timing of the event)

Table 4. Adverse Events

Characteristic	All Patients		Non-aspirin Cohort	
	Celecoxib 400 mg BID (n = 3995)	NSAIDs (n = 3987)	Celecoxib 400 mg BID (n = 3154)	NSAIDs (n = 3169)
Gastrointestinal				
Dyspepsia	14.4	18.0*	13.5	15.7*
Abdominal pain	9.7	13.1*	9.1	12.5*
Diarrhea	9.4	9.8	9.1	9.2
Nausea	6.9	9.3*	6.8	8.7*
Constipation	1.7	5.9*	1.5	5.4*
Withdrawals	10.8	13.8*	10.2	13.0*
Hepatic				
Elevated serum ALT or AST	0.9	3.2*	0.9	3.0*
Withdrawals	0.1	1.5*	0.1	1.4*
Bleeding-Related				
Anemia	2.2	4.4*	1.9	3.9*
Ecchymosis	0.7	0.8	0.7	0.8
Hematochezia	0.4	1.0*	0.3	0.9*
Withdrawals	0.3	0.6*	0.4	0.6
Renal				
Peripheral edema	2.8	3.5	2.9	3.4
[redacted]		Non-Resp.		
Increased creatinine	0.7	1.2*	0.6	1.0
Withdrawals	1.2	1.0	1.2	1.0
[redacted]		Non-Resp.		
Withdrawals	0.3	0.4	0.3	0.2
Cutaneous				
Rash	5.5	2.6*	5.7	2.9*
Pruritus	2.3	1.5*	2.3	1.4*
Urticaria	0.6	0.4	0.3	0.1
Withdrawals	3.1	1.3*	3.4	1.5*

Figure 1

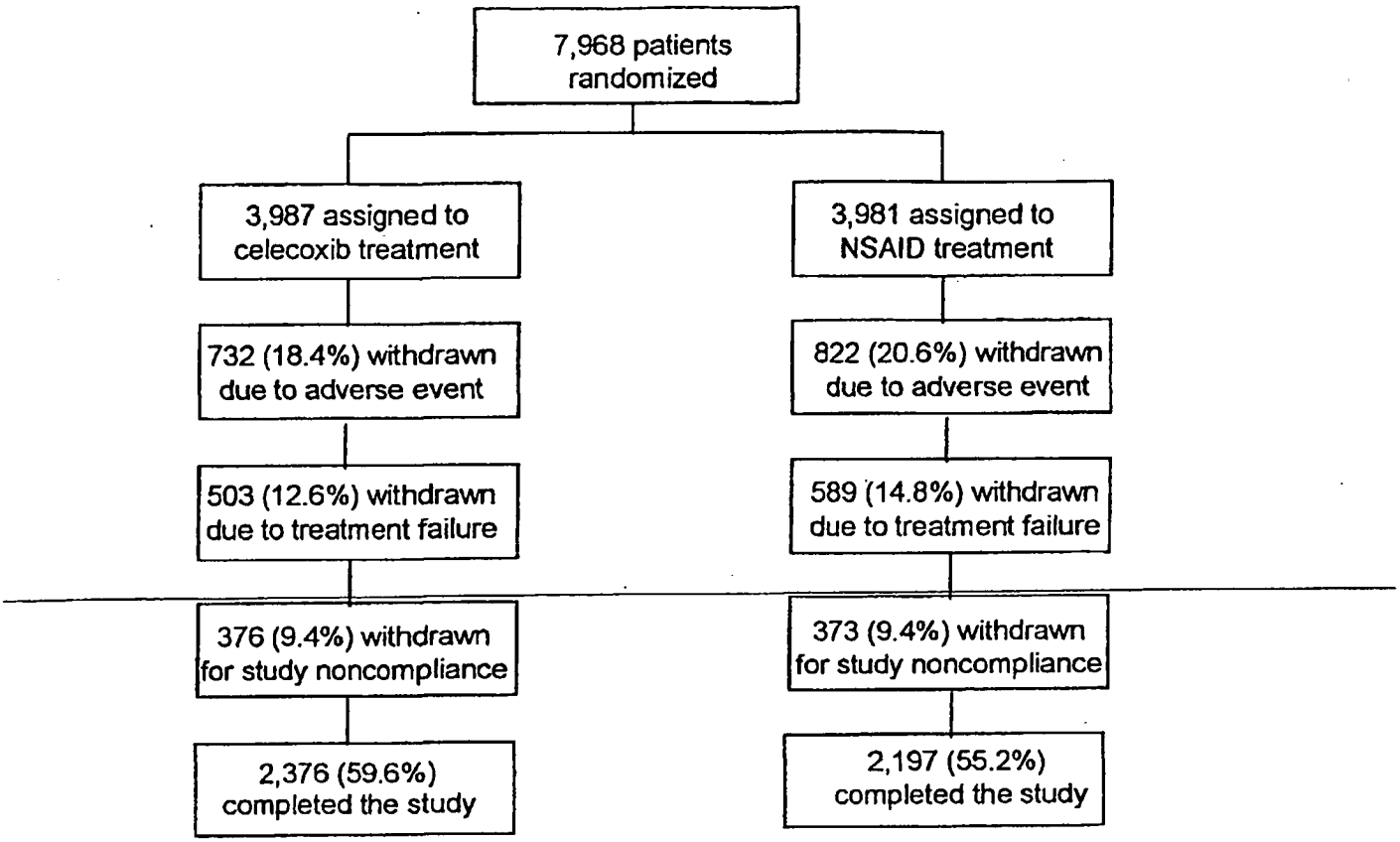

7,968 patients randomized
3,987 assigned to celecoxib treatment
3,981 assigned to NSAID treatment
732 (18.4%) withdrawn due to adverse event
822 (20.6%) withdrawn due to adverse event
503 (12.6%) withdrawn due to treatment failure
589 (14.8%) withdrawn due to treatment failure
376 (9.4%) withdrawn for study noncompliance
373 (9.4%) withdrawn for study noncompliance
2,376 (59.6%) completed the study
2,197 (55.2%) completed the study

EXHIBIT 152

EXHIBIT 68
DENISE D. BACH 7/27/10

LEFKOWITH, JAMES B. [PHR/1825]

From: express [JAMAEXPRESS@ama-assn.org]
Sent: Tuesday, July 18, 2000 2:01 PM
To: JAMES.B.LEFKOWITH@chi.monsanto.com
Subject: Re: RE: RE: FW: RE: RE: CLASS manuscript

Dear Dr Lefkowith,

Thank you for revising your manuscript for JAMA. We have discussed your manuscript and would like to continue to pursue it in an expedited fashion. However, we need some additional information. Please provide in a separate document (it is not necessary to include it the manuscript currently) the complete ITT analysis with all randomized patients included, to which you refer in your cover letter but which I couldn't find in the manuscript, and the results (not just P values) for the analyses including the censored patients (pages 12 and 13).

Also, please provide the number of patients who, prior to beginning the study, were taking the maximal doses of NSAIDs used in the study.

You state that the statistical analysis was performed by Pharmacia, yet there appears to be a statistician on your authorship list who is not at Pharmacia (Robert Makuch at Yale). What was his role? Were the authors who were not at Pharmacia involved with data analysis and interpretation as well, or did they just receive a copy of the already-analyzed data?

We appreciate your explanation for the rationale in using supraphysiological doses of celecoxib in this study. However, in the group taking ASA, the finding of no difference now makes these data difficult to interpret. Based on this analysis it would seem celecoxib provides no benefit, but since the doses aren't those used clinically it is difficult to say (although these are the best data available to answer the question). Were the supraphysiological doses required by FDA or was the study design determined solely by the company?

Finally, it appear on the authorship forms that you signed for Drs Verburg and Stephen Geis. Please have them complete the authorship form themselves.

Thank you for revising your manuscript and please contact me if you have any questions. I look forward to hearing from you.

Sincerely,

Margaret Winker, MD
Deputy Editor, JAMA
Director, Division of Scientific Online Resources

>>> "LEFKOWITH, JAMES B. [PHR/1825]"
<JAMES.B.LEFKOWITH@chi.monsanto.com> 07/10 7:41 PM >>>
Your fax was received. We appreciate the opportunity to respond to the concerns of the reviewers and will endeavor to have a completed response in
48 h.
JL

----Original Message----

Responses to Editorial Comments/Questions:

1. Patients who were randomized but not take drug did not contribute to either the number of events or the patient exposure. Therefore the annualized rates for this cohort are the same as those in the paper. The p values for the log rank tests for the Kaplan Meier analysis that includes such patients are also the same as those in the paper for the analysis that excludes such patients when rounded off to two decimal places. For the analysis which includes the censored events the annualized incidences are as follows:

Treatment	Ulcer complications +symptomatic ulcers	Ulcer complications
All Patients:		
Celecoxib	2.22% (32 events/1441 pt yrs)	0.90% (13 events/1441 pt yrs)
NSAIDs	3.69% (51 events/1384 pt yrs)	1.59% (22 evemts/1384 pt yrs)
Patients not on ASA:		
Celecoxib	1.49% (17 events/1143 pt yrs)	0.52% (6 events/1143 pt yrs)
NSAIDs	3.00% (33 events/1101 pt yrs)	1.36% (15 events/1101 pt yrs)
Patients on ASA:		
Celecoxib	5.03% (15 events/298 pt yrs)	2.35% (7 events/298 pt yrs)
NSAIDs	6.36% (18 events/283 pt yrs)	2.47% (7 events/283 pt yrs)

In preparing these rates, we would note that our internal reviewers failed to catch an error on pages 12 and 13 and Figure 1. The patient exposures for all patients and those not on ASA are incorrect whereas the patient exposures for patients on ASA are correct. The incidence rates are correct as are the statistical analyses. We regret the error and have corrected it in the accompanying manuscript.

2. The % (n) of patients on NSAIDs prior to study in each treatment group are:

Treatment	NSAID	Ibuprofen only	Diclofenac only
Celecoxib	81.4% (3246)	21.7% (866)	13.6% (543)
NSAID	81.6% (3252)	20.9% (834)	14.0% (556)

Given that patients on NSAIDs prior to study may be NSAID-tolerant, I would suggest that these data be added to Table 2 of the manuscript (Baseline Demographics) and have taken the liberty of doing so. Is this acceptable?

3. The non-Pharmacia authors served on the Executive Committee (F.S., L.S. and G.F.) as well as the GI Events Committee and DSMB. The members of these committees helped draft the protocol and the statistical analysis plan. The committees had defined roles (by charter) during the study that are partly described in the Methods section. In addition to monitoring trial safety and the accrual of GI events, the DSMB was empowered to view unblinded data should a safety concern arise or perform an interim analysis if required (according to protocol specifications) in private session (i.e. without Pharmacia participation). Dr. Makuch, the non-Pharmacia statistican, was to serve as the unblinded statistican for the DSMB in these circumstances. Such circumstances did not arise in the trial.

After completion of the trial, the statistical programming according to the statistical analysis plan was run at Pharmacia. The results from the closed database were then reviewed by a combined meeting of all the committees who had input both into the interpretation of the resulting data as well as the final display format of the locked and final dataset. The committee members also participated in the review of the resulting regulatory documents as well as the manuscript.

4. The decision to use a dose twice the maximally effective dose for RA and four times the maximally effective dose for OA was a mutual one. We at Pharmacia felt that using such a dose was necessary to establish that celecoxib has a unique mechanism of action and therapeutic ratio distinct from that of conventional NSAIDs. The FDA requested such a dose in order to stringently test the safety of the compound with respect to GI events.
5. The requested forms for Drs. Verburg and Geis will be faxed to you.

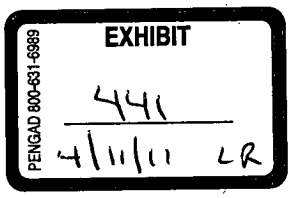
EXHIBIT 153

From: express [JAMAEXPRESS@ama-assn.org]
Sent: Tuesday, June 20, 2000 9:52 PM
To: JAMES.B.LEFKOWITH@chi.monsanto.com
Cc: KENNETH.M.VERBURG@chi.monsanto.com
Subject: CBX-0372836_Re: manscript submission from CLASS trial

CBX-0372837_ATT1
02554.txt

********** (on the network)

noname was scanned and no virus found
****



Dear Drs Lefkowith and Verburg,

Thank you for your message. As Dr Lefkowith and I discussed by phone on Monday, we would be pleased to evaluate your manuscript to determine whether it meets our criteria for JAMA-Express. You are welcome to send the manuscript as an e-mail attachment. Thank you for your interest in JAMA, and I look forward to hearing from you.

Sincerely,

Margaret Winker, MD
Deputy Editor, JAMA

>>> "LEFKOWITH, JAMES B. [PHR/1825]" <JAMES.B.LEFKOWITH@chi.monsanto.com> 06/19 5:04 PM >>>
Dear Dr. Winker-
As you may be aware, Pharmacia recently completed a large prospective outcome trial comparing celecoxib, the first specific cyclooxygenase-2 inhibitor, to conventional NSAIDs in terms of GI toxicity and other safety parameters. I discussed the possible submission of the resulting manuscript with Dr. Fontanarosa a number of months ago, and I am now pleased to follow up our conversation with a finalized manuscript which I would like to submit via the JAMA EXPRESS option on behalf of my colleagues.

We clearly feel that this manuscript contains important information regarding drug therapy for arthritis and is suitable for a general medical audience. If you concur, Dr. Verburg (copied on this email) will be happy to forward to you an electronic version for your consideration to start the process. Both Dr. Verburg and I clearly appreciate the energy required to complete this process and are more than happy to oblige you in terms of prompt replies along the timelines specified in the JAMA guidelines. Dr. Verburg will be the contact for this week as I will be in France attending EULAR. I will return on Saturday and can be reached 24 h a day by cell phone.

We look forward to your reply.

Regards,
James B. Lefkowith, MD

James B. Lefkowith, MD
Sr. Director, Searle R&D
4901 Searle Parkway
Skokie, IL 60077
847.982.4707
847.687.3154 (cell phone)
james.b.lefkowith@monsanto.com <mailto:james.b.lefkowith@monsanto.com>

EXHIBIT 154

From: JAMES B. LEFKOWITH at Exchange
Sent: Thursday, August 31, 2000 10:08 PM
To: Gandelman, Mitchell
Subject: RE: CONFIDENTIAL - Deeks review of CLASS.

MICHAEL FRIEDMAN
CCR
NO.: 302

We addressed this issue at High Wycombe on Tuesday. The review and manuscript
will be provided to NICE but not the study report. The decision was made to
withhold the study report pending review by the MPA and FDA. This decision was
made in concert with our EU Pharmacia and Pfizer colleagues who can fill you in.
The review, study report and manuscript are entirely consistent in my view. The
report is simply more comprehensive than the other two documents (and in many
respects more technical). The manuscript is the simplest version which treats
the NSAID groups as one. It would not be possible to write a manuscript as
comprehensive as the report.

I am not familiar with the people in the e-mail chain below. However, it is
R&D's purview to address questions regarding CLASS and we will continue to do so
along the lines we discussed today with Pfizer and Pharmacia by teleconference.
I suggest that it might be well for you to contact Mona Wahba and your EU
commercial colleagues to get caught up.
JL

-----Original Message-----
From: Mitchell Gandelman at NA1
Sent: Thursday, August 31, 2000 12:27 PM
To: LEFKOWITH, JAMES B. [PHR/1825]
Cc: LEVY, STEPHANE [PHR/1820]; Newell McElwee at NA1
Subject: FW: CONFIDENTIAL - Deeks review of CLASS.

Jim:

Can we discuss a plan to handle questions on any differences between the CLASS
Study Report and the JAMA Article? Below are E-mails discussing this topic as
regards the NICE (National Center for Clinical Excellence) submission in the UK.
The Nice submission was completed this month in the UK. NICE assesses the
clinical effectiveness and cost effectiveness of treatments, both
pharmacological and also other medical interventions. NICE assess the
intervention e.g. COX-2 inhibitors and decide whether or not to recommend NHS
usage in the UK. They are therefore a very significant institution. If they do
not recommend your product it will (to all intents and purposes) not be
prescribed on the NHS in the UK.

Sincerely,
Mitch

-----Original Message-----
From: McElwee, Newell
Sent: Thursday, August 31, 2000 7:31 AM
To: Gandelman, Mitchell
Subject: FW: CONFIDENTIAL - Deeks review of CLASS.

Pls handle as discussed. newell

-----Original Message-----
From: Bruce, Nick
Sent: Tuesday, August 29, 2000 10:15 AM
To: McElwee, Newell
Subject: RE: CONFIDENTIAL - Deeks review of CLASS.

Newell

Further to our conversation, it would be most useful if you could discuss Matt's comments with Jim Lefkwoth on our behalf and more generally how we can handle the differences between the study report / Deeks review and the ms. It would also be worth exploring with Jim his thoughts on how we introduce CLASS into the NICE submission. Given that the expidition process will put the ms into the public domain in Sept (rather than Jan/Feb 2001 as orignially anticipated) we are taking as a given that NICE will identify the ms. We also expect that NICE will ask for the study report in the same way they requested the P3 program study reports. In particular, what are the risks / benefits of proactively offer the Deeks report / study report ahead of NICE receiving the ms?

Thnaks
Nick

-----Original Message-----
From: McElwee, Newell
Sent: Monday, August 28, 2000 01:33
To: Bruce, Nick
Subject: RE: CONFIDENTIAL - Deeks review of CLASS.

thanks Nick. I will talk to Liz Kitsis and Mitch Gandelman tomorrow about this.
I think the authors of the JAMA publication should be ones addressing the discrepancies. Has anyone contacted Jim Leftkowith?

I'll be in the office on Tuesday, I'll arrange a time to call. n

-----Original Message-----
From: Bruce, Nick
Sent: Friday, August 25, 2000 12:10 PM
To: McElwee, Newell
Subject: CONFIDENTIAL - Deeks review of CLASS.
Importance: High

Hi Newell

I attach Jon Deeks review of the CLASS data based on the study report, carried out for us under confidentiality agreement. I also attach Matt's comparison of Jon's review and the forthcoming JAMA publication. This has highlighted a number of differences between the manuscript and the trial study report. With the expidited publication, it is very possible that NICE will ask for the CLASS study report in the same way that they requested the reports for the P3 programme. Pls can we discuss potential ways forward - Tuesday pm UK time would be good for me (Monday is a public holiday here).

Regards
Nick

<< File: Class update.doc >>

Matts comments

Please treat this information in confidence.

I have seen the pre-publication of the CLASS data that will be published in September, comments below show how this paper contrasts with Jon's recent report:

(a) The paper does not report the results for the two NSAIDs separately (when in fact they are very different)
(b) The paper fails to mention that trial follow-up was terminated early
(c) The non-aspirin subgroup is strongly emphasised (and better justified) in the paper than in the full trial report but not noted as a posthoc subgroup (this is not considered good practice in EBM circles)
(d) There is no discussion in the paper about the likely bias introduced by the differential drop-out in the two groups
(e) In the paper the adjusted analysis is not mentioned at all and yet this is probably the most powerful argument.
(f) Jon's full report contains a lot more information than you can gleam from the paper. If NICE got the paper (which they will) they are bound to ask for the study report, however if they received Jon's report it should contain everything they need and even if they were to ask for the study report they will at least have seen our interpretation first (this could be key in selling the adjustment analysis)
(g) There are some small differences in the figures between Jon's report and the paper- I suspect this is because the paper is based on "annualised incidence

rates" whilst Jon used the event rate at 6 months. None of the differences are
of importance, but worth noting.

EXHIBIT 155

From: Kitsis, Elizabeth
Sent: Thursday, August 31, 2000 9:44 PM
To: Gandelman, Mitchell
Subject: FW: CONFIDENTIAL - Deeks review of CLASS.

Mitch,
Spoke w/Joe about this.; Maybe we can follow up tomorrow. Thanks.
Liz

-----Original Message-----
From: Feczko, Joe
Sent: Monday, August 28, 2000 5:30 PM
To: Kitsis, Elizabeth; Sigmund, William
Subject: RE: CONFIDENTIAL - Deeks review of CLASS.

Liz

Not knowing the full report well the only point of differnece that seems somewhat relevant is the point 1---not reporting the two NSAIDs separately. Are they mentioned somewhat but not fully? I haven't had time to open this on the road but will look at it on my return. Off hand I don't think the descrepancies are that big of a problem. Authors ,especially if independent often put different interpretations. The issue of post hock analysis not being mentioned is not that critical. While EBM doesn't like it that is only an academic arguement for the purists.

Joe

-----Original Message-----
From: Kitsis, Elizabeth
Sent: Monday, August 28, 2000 4:32 PM
To: Feczko, Joe; Sigmund, William
Subject: FW: CONFIDENTIAL - Deeks review of CLASS.
Importance: High

FYI--this review was done by a consultant in preparation for the NICE submission. It was supported jointly by Pfizer and Pharmacia, with Pfizer taking the lead. I met with Newell, and we are ensuring that the information is provided to Pharmacia (Jim Lefkowith--corresponding author for CLASS). I can provide further background on this if you wish, but I just wanted to keep you in the loop.
Liz

-----Original Message-----
From: McElwee, Newell
Sent: Friday, August 25, 2000 9:27 PM
To: Kitsis, Elizabeth; Gandelman, Mitchell
Cc: Egbuonu-Davis, Lisa
Subject: FW: CONFIDENTIAL - Deeks review of CLASS.
Importance: High

MICHAEL FRIEDMAN
CCR
NO.: 303

It appears that there are discrepancies between the JAMA manuscript for CLASS and the CLASS study report. As I recall, the manuscript was submitted without Pfizer review. It seems likely that this discrepancy will emerge during the NICE review if NICE requests the CSR -- the JAMA article will be published on Sept 13. The external expert we used to prepare the clinical section of the NICE dossier (Jon Deeks from Oxford) will also be aware of this discrepancy as he has already seen the CSR. Any suggestions on how we handle this? Can we meet briefly on Monday to discuss?
Newell

-----Original Message-----
From: Bruce, Nick
Sent: Friday, August 25, 2000 12:10 PM
To: McElwee, Newell
Subject: CONFIDENTIAL - Deeks review of CLASS.
Importance: High

Hi Newell

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agreement. I also attach Matt's comparison of Jon's review and the forthcoming JAMA publication. This has highlighted a number of differences between the manuscript and the trial study report. With the expidited publication, it is very possible that NICE will ask for the CLASS study report in the same way that they requested the reports for the P3 programme. Pls can we discuss potential ways forward - Tuesday pm UK time would be good for me (Monday is a public holiday here).

Regards
Nick

<< File: Class update.doc >>

Matts comments

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